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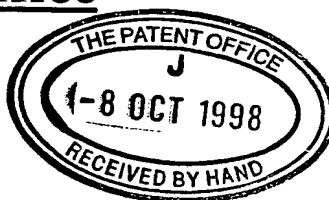
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Andrew Gersey

Dated 1 October 1999

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1. Your reference

KR/NM/P32152

09 OCT 98 E396060-1 D02029
F0177700 0.00 - 9821974.4

2. Patent application number

(The Patent Office will fill in his part)

08 OCT 1998

9821974.4

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

SMITHKLINE BEECHAM PLC
NEW HORIZONS COURT, BRENTFORD,
MIDDLESEX TW8 9EP

UNITED KINGDOM

5800974002

4. Title of the invention

Novel Method and Compounds

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number (if you know it)

CORPORATE INTELLECTUAL PROPERTY

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

4471231005

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

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Continuation sheets of this form
Description
Claim(s)
Abstract
Drawings

55

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 1/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature K Rutter Date 8-Oct-98

K Rutter

12. Name and daytime telephone number of person to contact in the United Kingdom

K Rutter 01279 644396

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Novel Method and Compounds

This invention relates to a novel method for the treatment of conditions associated with a need for inhibition of glycogen synthase kinase-3 (GSK-3), especially diabetes, dementias, such as Alzheimer's disease, manic depression and cancer and certain novel inhibitors of GSK-3 used in such method.

GSK-3 is a serine/threonine protein kinase having a 47kDa monomeric structure. It is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al* Eur. J. Biochem. (107) 519-527 (1980)). Two isoforms are found in mammalian cells: α and β . Both isoforms phosphorylate muscle glycogen synthase (Cross *et al* Biochemical Journal (303) 21-26 (1994)) and these two isoforms show good homology between species (e.g. human and rabbit GSK-3 α are 96% identical).

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage. The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J. Biochim. Biophys. Acta (39) 171-173 (1960), Parker P J *et al* Eur. J. Biochem. (130) 227-234 (1983), and Cohen P. Biochem. Soc. Trans. (21) 555-567 (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A K and Pandey S K Mol. and Cellular Biochem. (182) 135-141 (1998)).

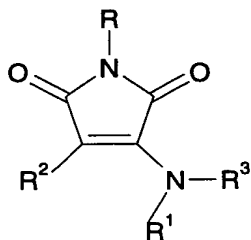
Chen *et al* Diabetes (43) 1234-1241 (1994) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type II diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3 α activity and insulin action (Nikoulina *et al* Glycogen Synthase Kinase-3 in Human Skeletal Muscle: Relationship To Insulin

Resistance in Type II Diabetes Diabetes (47(1)) 0028 Page A7 (1998) (Oral presentation)). Additionally, in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), overexpression of GSK-3 resulted in an impairment of insulin action (Eldar-Finkelman and Krebs PNAS (94) 9660-9664 (1997)).

GSK-3 has been shown to phosphorylate other proteins *in vitro*, e.g. Tau protein, which is hyperphosphorylated in Alzheimer's disease, and the eukaryotic initiation factor eIF-2B at Serine⁵⁴⁰. GSK-3 is known to be inhibited by lithium (Stambolic V., Ruel L. and Woodgett J.R. Curr. Biol. 1996 6(12): 1664-8) and lithium reduces the phosphorylation of tau, enhances the binding of tau to microtubules, and promotes microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M. J.Biol. Chem. 1997 272(40) 25326-32). WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is lithium, but that there are serious drawbacks associated with this treatment and the molecular mechanism underlying lithium's action for the treatment of manic depression has not been elucidated.

We have now discovered that certain substituted aminomaleimides are particularly potent and selective inhibitors of GSK-3. These compounds are therefore indicated to be useful for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, dementias, such as Alzheimer's disease, manic depression and cancer. Certain of these compounds are novel and such compounds comprise a further aspect of the invention.

Accordingly, in a first aspect the present invention provides a method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, dementias, such as Alzheimer's disease, manic depression and cancer, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof, wherein:

R is hydrogen, alkyl, aryl, or aralkyl;

R¹ is hydrogen, alkyl, aralkyl or alkoxyalkyl;

R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;
 R^3 is hydrogen, alkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or

R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocyclic ring, to a human or non-human mammal in need thereof.

Suitably, R is hydrogen.

Suitably, R^1 is hydrogen.

Suitably, R^2 is phenyl or naphthyl or substituted phenyl or substituted naphthyl, wherein substituents for the phenyl or naphthyl group are selected from up to three of C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxymethyl, halo, hydroxy, carboxy, cyano, nitro, C_{1-6} alkylthio, trifluoromethyl, trifluoromethyloxy, trifluoromethylthio, phenoxy, phenyl, benzyloxy and methylenedioxy.

Favourably, R^2 is phenyl either unsubstituted or substituted with up to three of methyl, methoxy, chloro or nitro.

Suitably, R^3 is phenyl either unsubstituted or substituted by up to three of C_{1-6} alkyl, phenyl, naphthyl, benzyl, C_{1-6} alkoxy, phenyloxy, phenylthio, carboxy C_{1-6} alkylthio carboxyphenylthio, benzyloxy, C_{1-6} alkylthio, halo, hydroxy, carboxy, cyano, nitro, acyl, hydroxymethyl, hydroxyethyl, trifluoromethyl, trifluoromethyloxy, trifluoromethylthio, trityl, carboxymethyl, cyanomethyl, carboxy C_{1-6} alkyloxy, C_{2-6} alkenyl, carboxy C_{2-6} alkenyl, carbamoyl, carbamoyl C_{1-6} alkyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylcarbonylalkylamino, C_{1-6} alkylaminosulphonylalkyl, mono- or bis-alkylphosphonate C_{1-6} alkyl, morpholinyl, adamantyl, oxazolyl and methylenedioxy or any two adjacent substituents on the phenyl ring together with the carbon atoms to which they are attached form a 5 or 6 membered carbocyclic ring or a 5 or 6 membered heterocyclic ring.

Favourably, R^3 is phenyl either unsubstituted or substituted with up to three of methyl, propyl, butyl, n-butoxy, phenoxy, thiomethyl, halo, hydroxy, benzyl, benzoyl, acetyl, 2-carboxyethenyl or any two adjacent substituents on the phenyl ring together with the carbon atoms to which they are attached form a fused cyclopentyl ring or a fused thiazolyl ring.

When R^1 and R^3 together with the nitrogen to which they are attached form a heterocyclic ring, suitable rings include unsaturated rings having 5 to 8 ring atoms, such as imidazolyl.

When R^1 and R^3 together with the nitrogen to which they are attached form a heterocyclic ring, suitable rings include saturated rings having 5 to 8 ring atoms, such as pyrrolidinyl, piperidinyl or azepinyl.

Suitable optional substituents for any heterocyclic ring represented by NR^1R^3 includes up to three of alkyl, hydroxy, nitro, carbamoyl, hydroxy(C_{1-4})alkyl or aryl(C_{1-4})alkyl or any two adjacent substituents of the ring, together with the carbon atoms to which they are attached, form a benzene ring.

There is a sub-group of compounds, falling wholly within formula (I), and being of formula (IA), wherein R , R^1 , R^2 and R^3 are as defined in relation to formula (I), with the proviso that formula (IA) does not include:

- 3-indol-1-yl-4-(1-methyl-1*H*-indol-3-yl)-pyrrole-2,5-dione;
- 1-(1-methyl-2,5-dioxo-4-phenylamino-2,5-dihydro-1*H*-pyrrol-3-yl)pyridinium chloride;
- 1-[1-(4-methyl-pentyl)-2,5-dioxo-4-phenylamino-2,5-dihydro-1*H*-pyrrol-3-yl]pyridinium chloride;
- 1-(1-dodecyl-2,5-dioxo-4-phenylamino-2,5-dihydro-1*H*-pyrrol-3-yl)-pyridinium chloride;
- 3-[2-benzo[b]thien-2-yl-3-[4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1*H*-pyrrol-3-yl]-1*H*-indol-1-yl]-carbamimidothioic acid, propyl ester;
- 3-(dimethylamino)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-indol-3-yl)-1-methyl-4-(phenylamino)-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-indol-3-yl)-1-methyl-4-[[4-(trifluoromethyl)phenyl]amino]-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-indol-3-yl)-1-methyl-4-(methylamino)-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-imidazo[4,5-*b*]pyridin-1-yl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 3-(6-chloro-9*H*-purin-9-yl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 3-(6-amino-9*H*-purin-9-yl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-indol-3-yl)-1-methyl-4-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-indol-3-yl)-1-methyl-4-(1-piperidinyl)-1*H*-pyrrole-2,5-dione;
- 3-[4-(diphenylmethyl)-1-piperazinyl]-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 1-acetyl-3-[2,5-dihydro-1-methyl-2,5-dioxo-4-[[4-(trifluoromethyl)phenyl]amino]-1*H*-pyrrol-3-yl]-1*H*-indole;
- 3-(1*H*-benzimidazol-1-yl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-benzotriazol-1-yl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione;
- 3-(1*H*-imidazol-1-yl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione

3-(1H-indol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione
 3-(1H-indazol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-[3-[(dimethylamino)methyl]-1H-indol-1-yl]-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(1H-indol-1-yl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione;
 3-(1H-benzimidazol-1-yl)-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione; and
 3-(1H-indol-1-yl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione.

There is a further sub-group of compounds, falling wholly within formula (I), and being of formula (IB), wherein R, R¹, R² and R³ are as defined in relation to formula (I), with the proviso that formula (IB) does not include:

3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione;
 3-phenyl-4-piperidin-1-yl-pyrrole-2,5-dione;
 3-(4-methylpiperazin-1-yl)-4-phenyl-pyrrole-2,5-dione;
 3-(4-ethylpiperazin-1-yl)-4-phenyl-pyrrole-2,5-dione;
 3-(4-chlorophenyl)-4-(4-methylpiperazin-1-yl)-pyrrole-2,5-dione;
 3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-4-morpholin-4-yl-pyrrole-2,5-dione;
 3-indol-1-yl-4-(1-methyl-1H-indol-3-yl)-pyrrole-2,5-dione;
 1,3-dimethyl-4-methylaminopyrrole-2,5-dione;
 1-(1-methyl-2,5-dioxo-4-phenylamino-2,5-dihydro-1H-pyrrol-3-yl)-pyridinium chloride;
 1-1-(4-methyl-pentyl)-2,5-dioxo-4-phenylamino-2,5-dihydro-1H-pyrrol-3-yl)-pyridinium chloride;
 1-(1-dodecyl-2,5-dioxo-4-phenylamino-2,5-dihydro-1H-pyrrol-3-yl)-pyridinium chloride;
 3-[2,5-dihydro-4-(1H-imidazol-1-yl)-1-methyl-2,5-dioxo-1H-pyrrol-3-yl]-1H-indole-1-carboxylic acid, 1,1-dimethylethyl ester;
 3-[2-benzo[b]thien-2-yl-3-[4-(dimethylamino)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl]-1H-indol-1-yl]-carbamimidothioic acid, propyl ester;
 3-(dimethylamino)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(1H-indol-3-yl)-1-methyl-4-(phenylamino)-1H-pyrrole-2,5-dione;
 3-(1H-indol-3-yl)-1-methyl-4-[[4-(trifluoromethyl)phenyl]amino]-1H-pyrrole-2,5-dione;
 3-(1H-indol-3-yl)-1-methyl-4-(methylamino)-1H-pyrrole-2,5-dione;
 3-(1H-imidazo[4,5-b]pyridin-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(6-chloro-9H-purin-9-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(6-amino-9H-purin-9-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;

3-(1H-indol-3-yl)-1-methyl-4-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrrole-2,5-dione;
 3-(1H-indol-3-yl)-1-methyl-4-(1-piperidinyl)-1H-pyrrole-2,5-dione;
 3-[4-(diphenylmethyl)-1-piperazinyl]-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 1-acetyl-3-[2,5-dihydro-1-methyl-2,5-dioxo-4-[[4-(trifluoromethyl)phenyl]amino]-1H-pyrrol-3-yl]-1H-indole;
 3-(1H-benzimidazol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(1H-benzotriazol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(1H-imidazol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione
 3-(1H-indol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione
 3-(1H-indazol-1-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-[3-[(dimethylamino)methyl]-1H-indol-1-yl]-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione;
 3-(1H-indol-1-yl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione;
 3-(1H-benzimidazol-1-yl)-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione;
 3-(1H-indol-1-yl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione;
 3,3'-iminobis[1-methyl-4-(4-methylphenyl)-1H-pyrrole-2,5-dione;
 1-[4-(2,3-dihydro-1,3-dioxo-1H-inden-2-yl)-2,5-dihydro-2,5-dioxo-1H-pyrrol-3-yl]pyridinium internal salt;
 1-[4-(2,3-dihydro-1,3-dioxo-1H-inden-2-yl)-2,5-dihydro-1-methyl-2,5-dioxo-1H-pyrrol-3-yl]pyridinium internal salt; and
 3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-4-(4-morpholinyl)-1H-pyrrole-2,5-dione.

It is considered that the compounds of formula (IB) are novel. Accordingly, the present invention also provides a compound of the above defined formula (IB) or a derivative thereof.

Certain of the compounds of formula (I) may contain at least one chiral carbon, and hence they may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including racemates.

Alkyl groups referred to herein, including those forming part of other groups, include straight or branched chain alkyl groups containing up to six carbon atoms, said carbon atoms being optionally substituted with up to five, suitably up to three, groups selected from the list consisting of aryl, heterocyclyl, alkylthio, alkenylthio, alkynylthio, arylthio, heterocyclylthio, alkoxy, arylalkoxy,

arylalkylthio, amino, mono- or di-alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, hydroxy, and halogen.

Alkenyl and alkynyl groups referred to herein include straight and branched chain alkenyl groups containing from two to six carbon atoms, said carbon atoms being optionally substituted with up to five, suitably up to three, groups including those substituents described hereinbefore for the alkyl group.

Cycloalkyl and cycloalkenyl groups referred to herein include groups having between three and eight ring carbon atoms, which carbon atoms are optionally substituted with up to five, suitably up to three, groups including those substituents described hereinbefore for the alkyl group.

When used herein the term "aryl" includes phenyl and biphenyl groups, for example naphthyl, especially phenyl.

Suitably optional substituents for any aryl group include up to three substituents selected from the list consisting of halo, alkyl, alkenyl, substituted alkenyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkyloxy, hydroxy, hydroxyalkyl, nitro, amino, cyano, cyanoalkyl, mono- and di-*N*-alkylamino, acyl, acylamino, *N*-alkylacylamino, acyloxy, carboxy, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkenyl, ketoalkylester, carbamoyl, carbamoylalkyl, mono- and di-*N*-alkylcarbamoyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy, arylthio, aralkyloxy, aryloxycarbonyl, ureido, guanidino, morpholino, adamantyl, oxazolyl, aminosulphonyl, alkylaminosulphonyl, alkylthio, haloalkylthio, alkylsulphanyl, alkylsulphonyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, trityl, substituted trityl, mono- or bis-alkylphosphonate or mono- or bis-alkylphosphonateC₁₋₆alkyl or any two adjacent substituents on the phenyl ring together with the carbon atoms to which they are attached form a carbocyclic ring or a heterocyclic ring.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Substituents for any heterocyclyl or heterocyclic group are suitably selected from halogen, alkyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, hydroxy, amino, mono- and di-*N*-alkyl-amino, acylamino, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-alkylcarbonyl, aryloxycarbonyl, alkoxycarbonylalkyl,

aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, heterocyclyl and heterocyclalkyl.

When used herein 'halo' includes iodo, bromo, chloro or fluoro, especially chloro or fluoro.

Suitable derivatives of the compounds of the invention are pharmaceutically acceptable derivatives.

Suitable derivatives of the compounds of the invention include salts and solvates.

Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

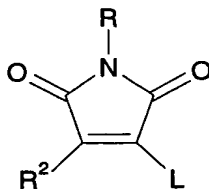
Suitable pharmaceutically acceptable salts also includes pharmaceutically acceptable acid addition salts, such as those provided by pharmaceutically acceptable inorganic acids or organic acids.

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable inorganic acids includes the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and hydroiodide.

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable organic acids includes the acetate, tartrate, maleate, fumarate, malonate, citrate, succinate, lactate, oxalate, benzoate, ascorbate, methanesulphonate, α -keto glutarate and α -glycerophosphate.

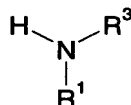
Suitable pharmaceutically acceptable solvates include hydrates.

A further aspect of the invention provides a process for the preparation of a compound of the invention, which process comprises reaction of a compound of formula (II):



(II)

wherein R and R² are as defined in formula (I) and L is a leaving group, with a compound of formula (III):



(III)

wherein R¹ and R³ are as defined in formula (I); and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compounds of formulae (II) and (III) is carried out in any suitable solvent, for example 1-methyl-2-pyrrolidinone or methanol, under conventional amination conditions at any temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time.

Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. Conventional methods of heating also include the use of microwave heating devices, for example a microwave reactor, such as a 100 watt reactor.

The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the residue acidified and the products extracted using solvent extraction, suitably using an organic solvent.

The reaction products are purified by conventional methods, such as chromatography and trituration.

Crystalline product may be obtained by standard methods.

In a preferred aspect, a solution of the compound of formula (II) and a compound of formula (III) in methanol is heated to reflux from between 1 to 4 days, then cooled and concentrated. The residue is then acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extracts are then washed with water, brine, dried with anhydrous magnesium sulphate, and the solvent is removed. The product is then purified by standard methods such as trituration or chromatography, on silica gel, to afford the desired compound.

The above mentioned conversion of a compound of formula (I) into a further compound of formula (I) includes converting one group R into another group R.

The said conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure. For example, conversion of one group R into another group R includes converting a group R which represents hydrogen into a group R which represents an alkyl or arylalkyl group; such conversion may be carried out using an appropriate conventional alkylation procedure, for example treating an appropriately protected compound of formula (I) with an alkylating agent.

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional chemical procedures.

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The derivatives of the compounds of formula (I), including salts and/or solvates, may be prepared and isolated according to conventional procedures.

The compounds of formula (II) are known compounds or they may be prepared using methods analogous to those used to prepare such compounds such as those described in International Patent Application, Publication Number WO97/34890 and Wiley, R.H. and Slaymaker, S.C. J. Am. Chem. Soc. (80) 1385 (1958). The compounds of formula (II) may be inter-converted in an analogous manner to the above mentioned inter-conversions of the compounds of formula (I).

The compounds of formula (III) are known commercially available compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in standard reference

texts of synthetic methodology such as J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

As stated above, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

Thus the present invention further provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of glycogen synthase kinase-3, such as diabetes, dementias, such as Alzheimer's disease, manic depression and cancer.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of glycogen synthase kinase-3, such as diabetes, dementias, such as Alzheimer's disease, manic depression and cancer.

As indicated above, formula (I) comprises a sub-group of compounds of formula (IA). In a further aspect of this invention, there is provided a compound of formula (IA), or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (IA), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

Preferably, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof are administered as pharmaceutically acceptable compositions.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for

example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to

ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

GSK-3 Assay: The GSK-3 specific peptide used in this assay was derived from the phosphorylation site of glycogen synthase and its sequence is: YRRAAVPPSPSLSRHSSPHQ(S)EDEEE. (S) is pre-phosphorylated as is glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The buffer used to make up the glycogen synthase peptide and [γ -³³P] ATP consisted of MOPS 25mM, EDTA 0.2mM, MgAcetate 10mM, Tween-20 0.01% and mercaptoethanol 7.5mM at pH 7.00.

The compounds were dissolved in dimethyl sulphoxide (DMSO) to a final concentration of 100mM. Various concentrations were made up in DMSO and mixed with the substrate (GSK-3 peptide) solution (to a final concentration 20uM) described in the above section along with rabbit GSK-3 α (final concentration 0.5U/ml enzyme). The reactions were initiated with the addition of [γ -³³P] ATP (500cpm/pmole) spiked into a mixture of ATP (final concentration of 10uM). After 30 min at room temperature the reaction was terminated by the addition of 10uL of H₃PO₄ / 0.01% Tween-20 (2.5%). A volume (10uL) of the mixture was spotted onto P-30 phosphocellulose paper (Wallac & Berthold, EG&G Instruments Ltd, Milton Keynes). The paper was washed four times in H₃PO₄ (0.5%), 2 mins for each wash, air dried and the radioactive phosphate incorporated into the synthetic glycogen synthase peptide, which binds to the P-30 phosphocellulose paper, was counted in a Wallac microbeta scintillation counter.

Analysis of Data: Values for IC₅₀ for each inhibitor were calculated by fitting a four-parameter logistic curve to the model : $cpm = lower + (upper - lower) / (1 + (concentration / IC_{50})^{slope})$. The most potent compounds of the present invention show IC₅₀ values in the range of from between 10 to 100 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Examples illustrate the invention, but do not limit it in any way.

Example 1**3-(3-Bromophenylamino)-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione**

A solution of 3-bromoaniline (2.27 mL, 0.020 mol) and 3-chloro-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione (2.02 g, 0.0083 mol; prepared by analogy with the methods described in WO97/34890 and Wiley, R.H. and Slaymaker, S.C. J. Am. Chem. Soc. (80) 1385 (1958)) in methanol (50 mL) was heated at reflux for 40 hours, cooled and concentrated. The residue was acidified with aqueous hydrochloric acid (1M, 200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic solutions were washed with water and brine, dried with magnesium sulphate, evaporated and the residue chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 100:0 to 95:5 v/v) as eluent to afford the title compound as a solid.

^1H NMR (DMSO- d_6): δ 6.70-7.30 (8H, m), δ 9.65 (1H, br), δ 10.90 (1H, br).

MS (APCI +ve): $[\text{M}+\text{H}]^+$ at m/z 377/379/381 ($\text{C}_{16}\text{H}_{10}\text{BrClN}_2\text{O}_2$ requires $[\text{M}+\text{H}]^+$ at m/z 377/379/381).

Example 2**3-(4-Benzoylphenylamino)-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione**

A sealed tube (comprising threaded glass tube with resealable cap) containing a mixture of 4-aminobenzophenone (0.147 g, 0.75 mmol), 3-chloro-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione (0.061 g, 0.25 mmol) and 1-methyl-2-pyrrolidinone (0.5 mL) was irradiated in a microwave reactor for 12 minutes at 100 Watts. The mixture was diluted with aqueous hydrochloric acid (5 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic solutions were evaporated and the residue chromatographed on silica gel using dichloromethane as eluent to afford the title compound as a solid.

^1H NMR (DMSO- d_6): δ 6.85 (2H, d), δ 7.00 (2H, d), δ 7.25 (2H, d), δ 7.35 (2H, d), δ 7.50-7.70 (5H, m), δ 9.95 (1H, s), δ 10.95 (1H, s)

MS (APCI -ve): $[\text{M}]^-$ at m/z 402/404 ($\text{C}_{23}\text{H}_{15}\text{ClN}_2\text{O}_3$ requires $[\text{M}]^-$ at m/z 402/404)

Example 3**3-(3-Bromo-4-methylphenylamino)-4-(3-nitrophenyl)-1H-pyrrole-2,5-dione**

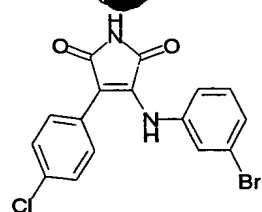
A mixture of 3-bromo-4-methylaniline (0.220 g, 1.18 mmol), 3-chloro-4-(3-nitrophenyl)-1H-pyrrole-2,5-dione (0.100 g, 0.40 mmol) and 1-methyl-2-pyrrolidinone (1.0 mL) was heated in an oil bath at 200°C for 51 minutes. The mixture was diluted with aqueous hydrochloric acid (5 mL) and extracted with ethyl acetate (5 mL). The combined organic solutions were evaporated and the residue chromatographed on silica gel using dichloromethane as eluent to afford the title compound, a solid, following trituration with dichloromethane-hexane (90:10 v/v).

¹H NMR (CDCl₃): δ2.24 (3H, s), δ6.65-7.70 (7H, m, reduces to 5H on D₂O exchange), δ8.05 (2H, m)

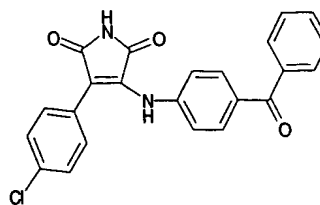
MS (APCI -ve): [M-H]⁻ at m/z 400/402 (C₁₇H₁₂BrN₃O₄ requires [M-H]⁻ at m/z 400/402).

The further examples described herein were prepared according to the methods disclosed herein, with particular reference to Examples 1 to 3 above.

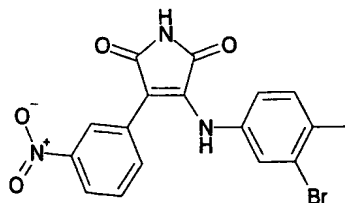
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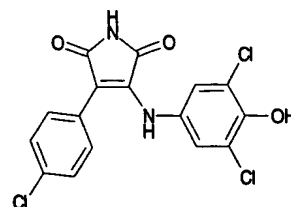
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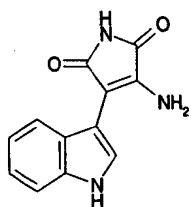
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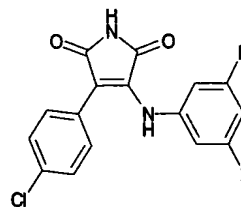
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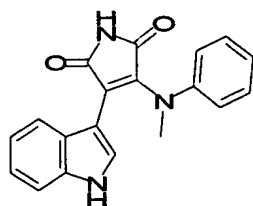
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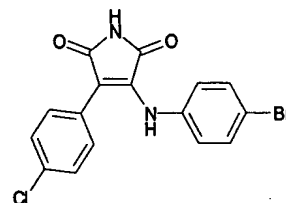
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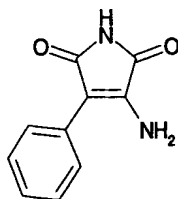
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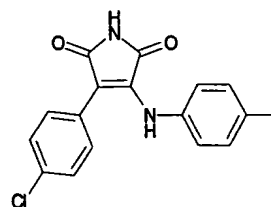
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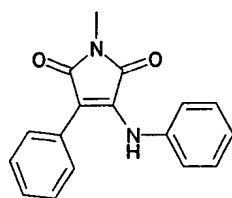
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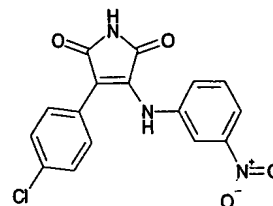
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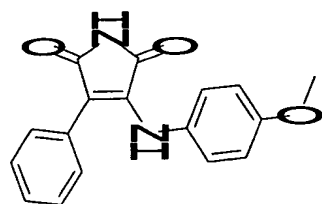
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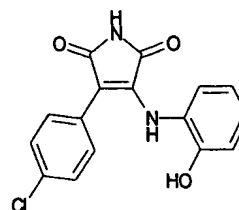
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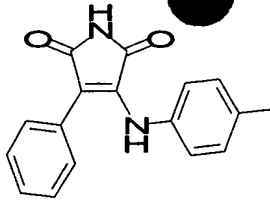
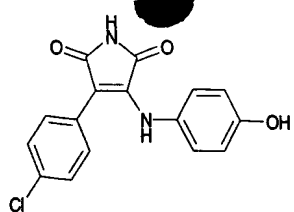
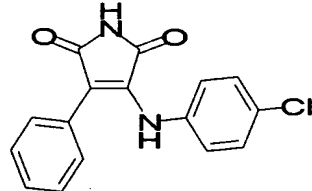
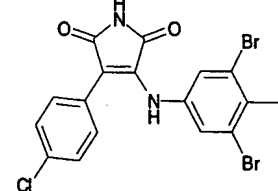
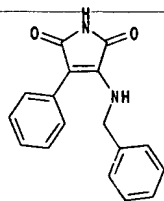
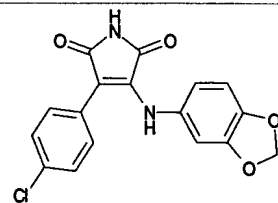
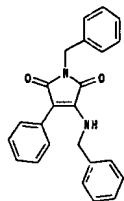
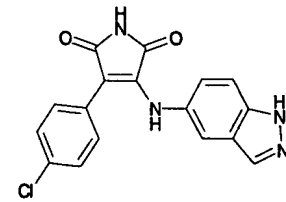
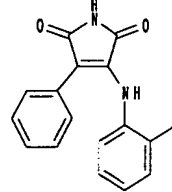
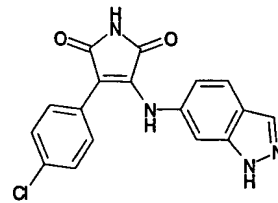
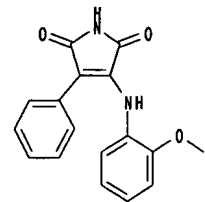
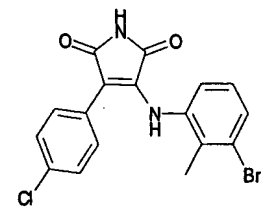
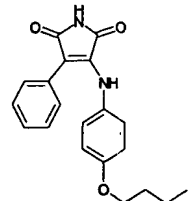
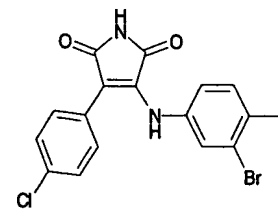


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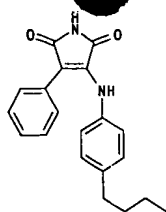


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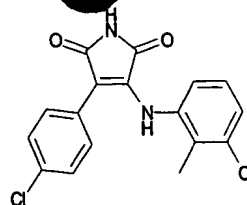


Ex 15		Ex 16	
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Ex 19		Ex 20	
Ex 21		Ex 22	
Ex 23		Ex 24	
Ex 25		Ex 26	
Ex 27		Ex 28	

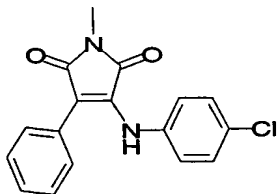
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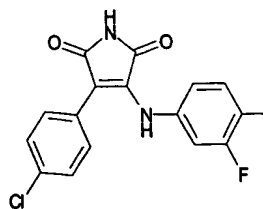
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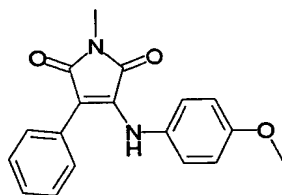
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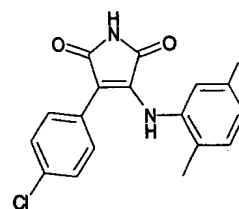
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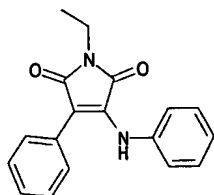
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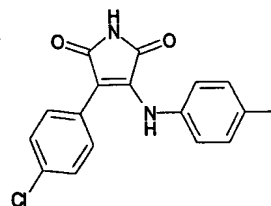
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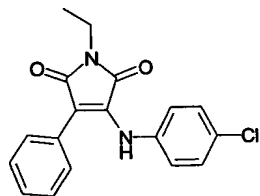
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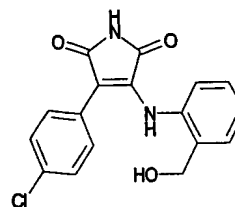
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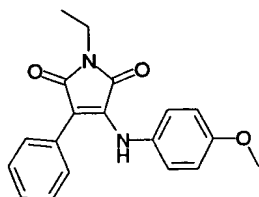
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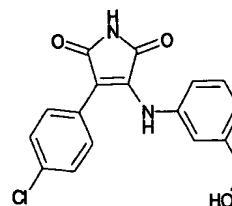
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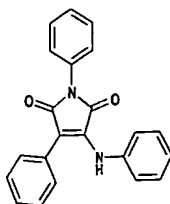
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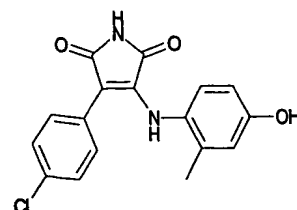
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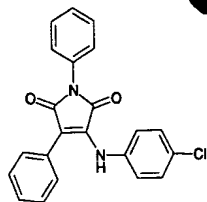
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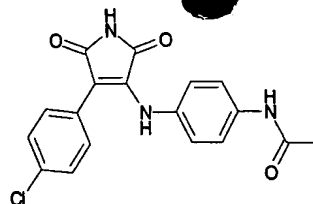
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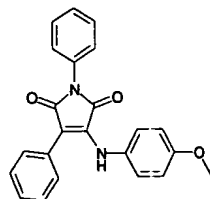
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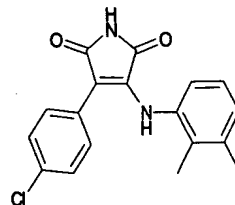
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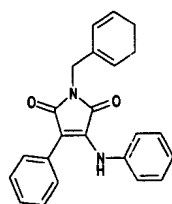
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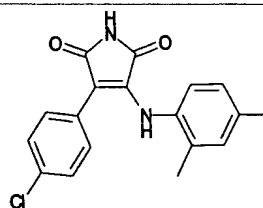
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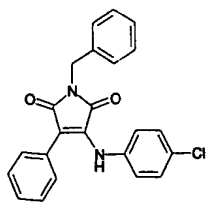
Ex 47



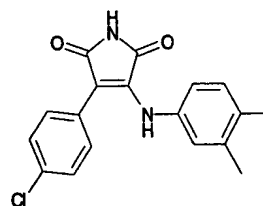
Ex 48



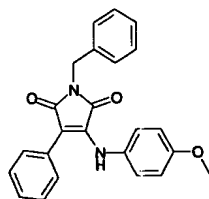
Ex 49



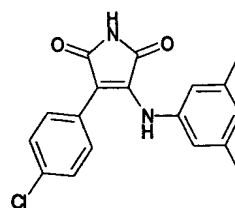
Ex 50



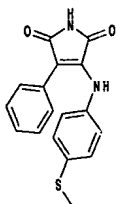
Ex 51



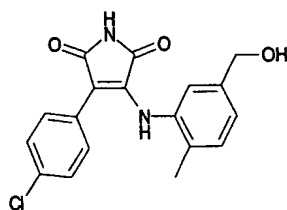
Ex 52



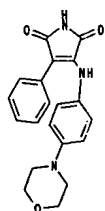
Ex 53



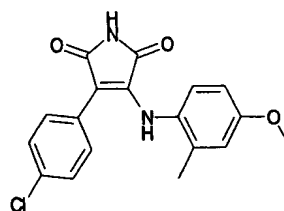
Ex 54



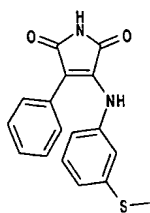
Ex 55



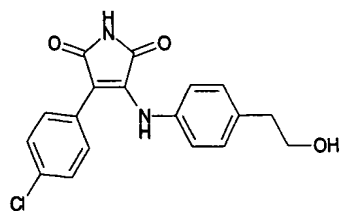
Ex 56



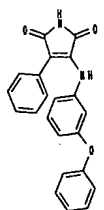
Ex 57



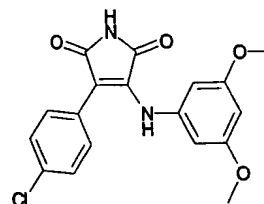
Ex 58



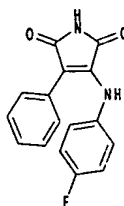
Ex 59



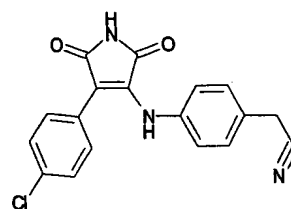
Ex 60



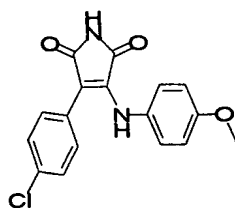
Ex 61



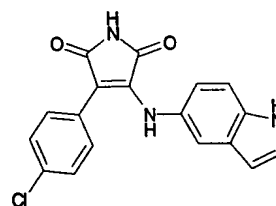
Ex 62



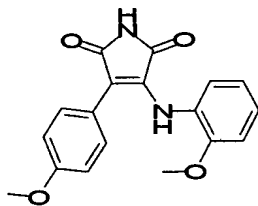
Ex 63



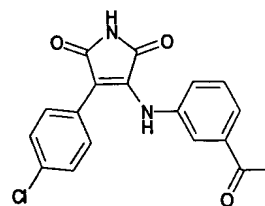
Ex 64



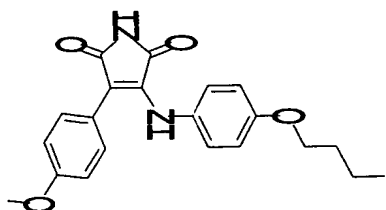
Ex 65



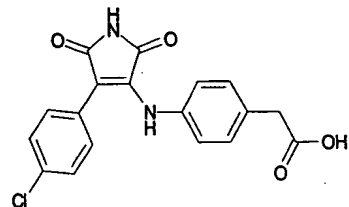
Ex 66



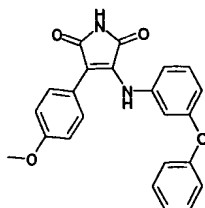
Ex 67



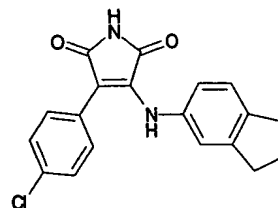
Ex 68



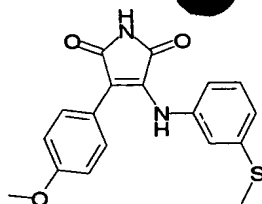
Ex 69



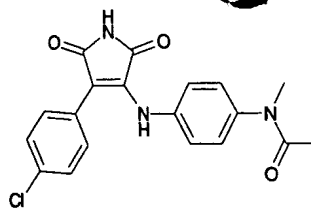
Ex 70



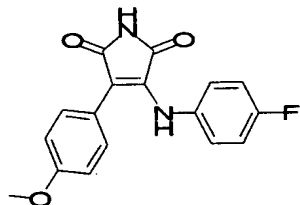
Ex 71



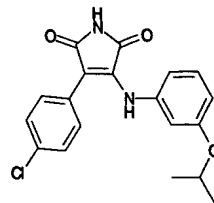
Ex 72



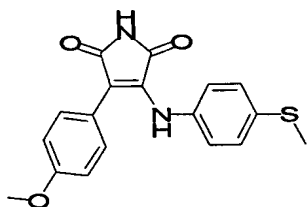
Ex 73



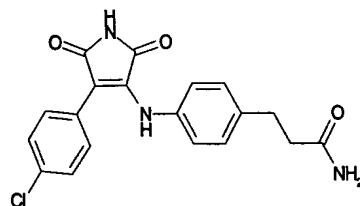
Ex 74



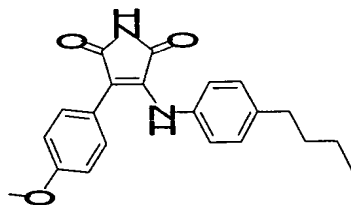
Ex 75



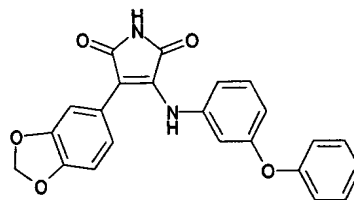
Ex 76



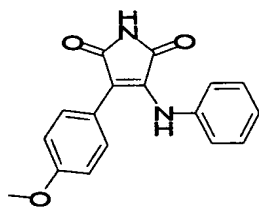
Ex 77



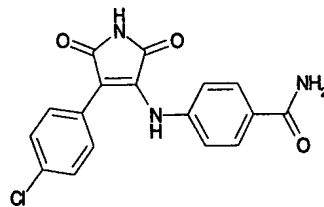
Ex 78



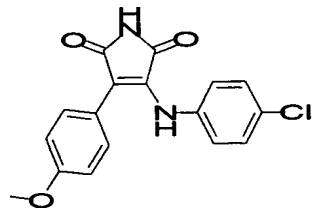
Ex 79



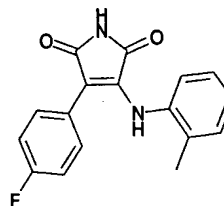
Ex 80



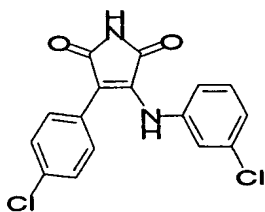
Ex 81



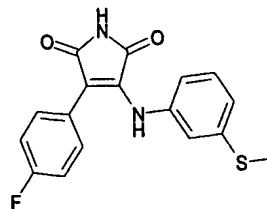
Ex 82



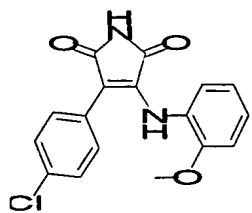
Ex 83



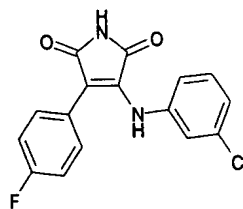
Ex 84



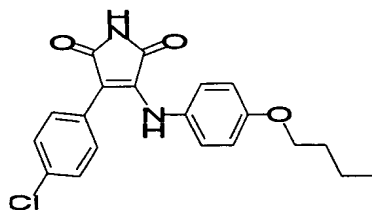
Ex 85



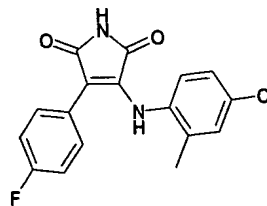
Ex 86



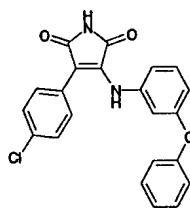
Ex 87



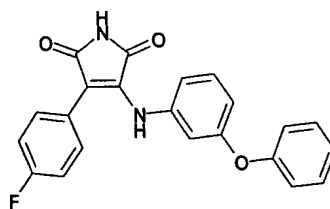
Ex 88



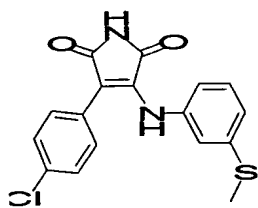
Ex 89



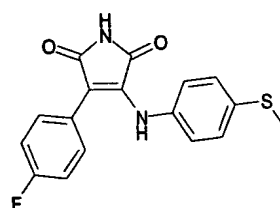
Ex 90



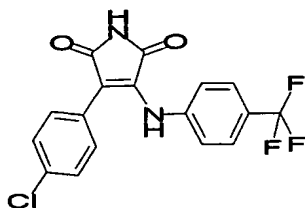
Ex 91



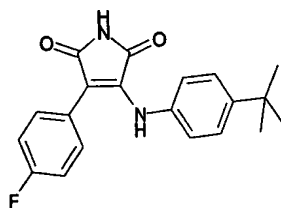
Ex 92



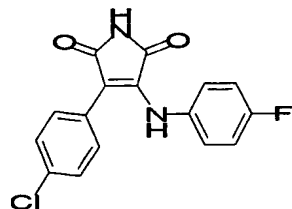
Ex 93



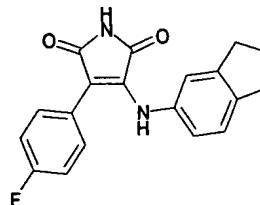
Ex 94



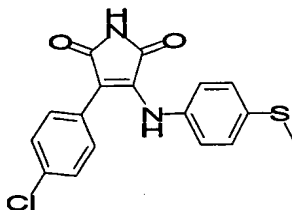
Ex 95



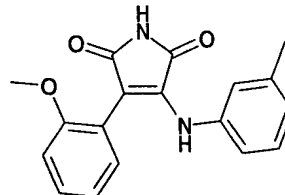
Ex 96



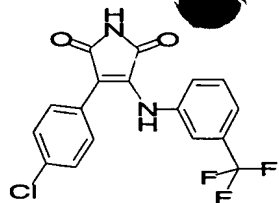
Ex 97



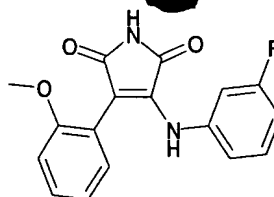
Ex 98



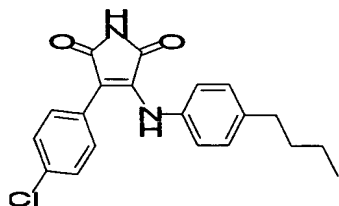
Ex 99



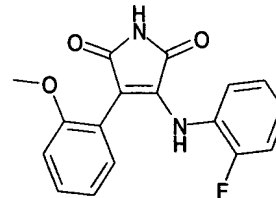
Ex 100



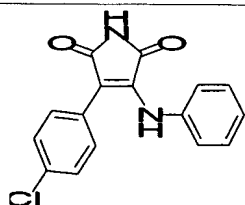
Ex 101



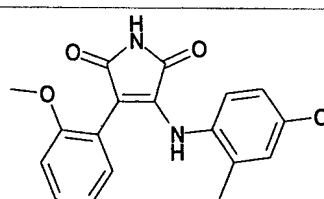
Ex 102



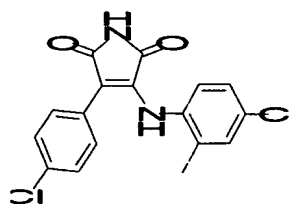
Ex 103



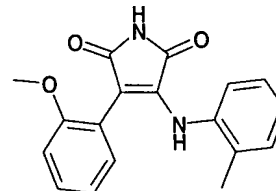
Ex 104



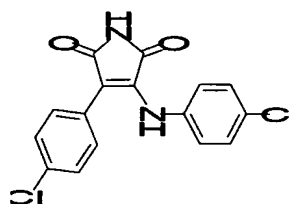
Ex 105



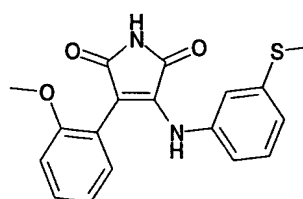
Ex 106



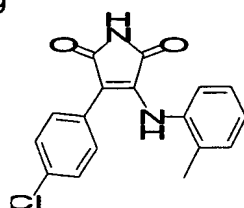
Ex 107



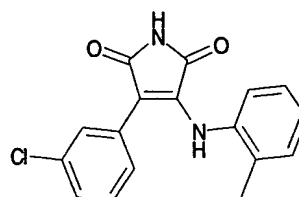
Ex 108



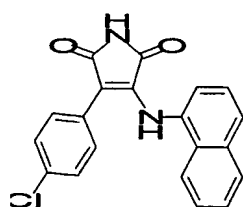
Ex 109



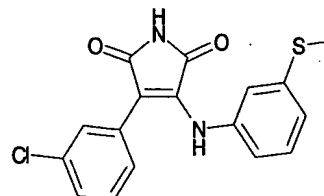
Ex 110



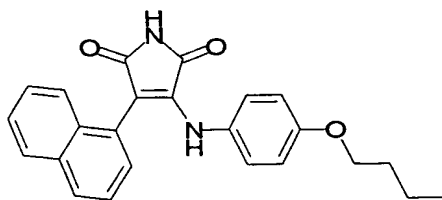
Ex 111



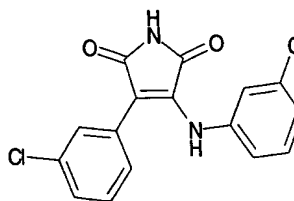
Ex 112



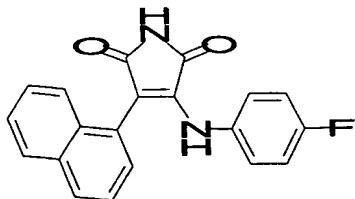
Ex 113



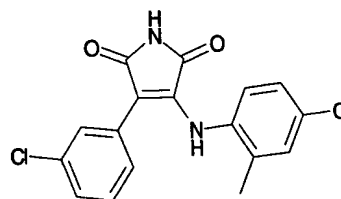
Ex 114



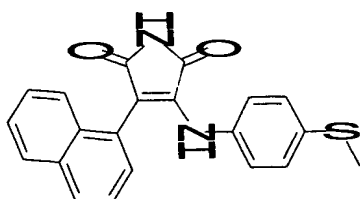
Ex 115



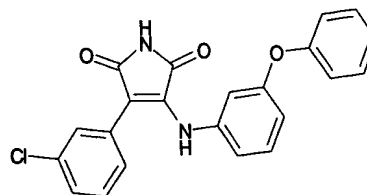
Ex 116



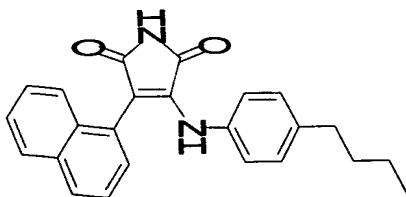
Ex 117



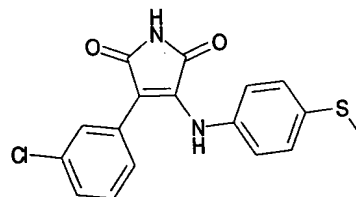
Ex 118



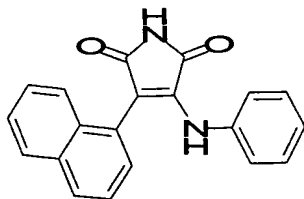
Ex 119



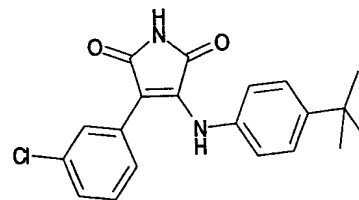
Ex 120



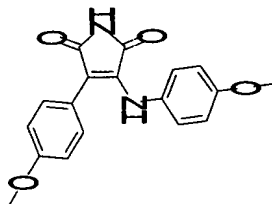
Ex 121



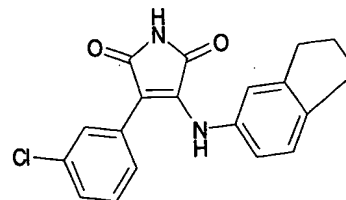
Ex 122



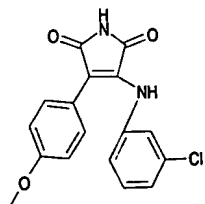
Ex 123



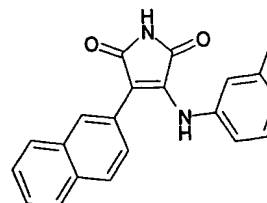
Ex 124



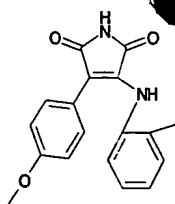
Ex 125



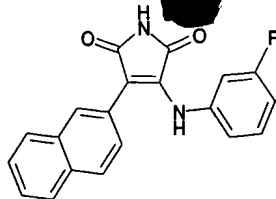
Ex 126



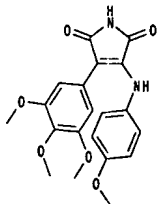
Ex 127



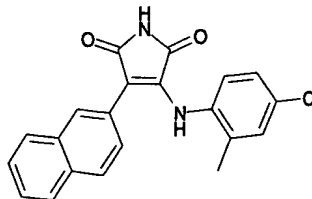
Ex 128



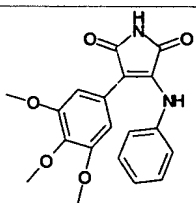
Ex 129



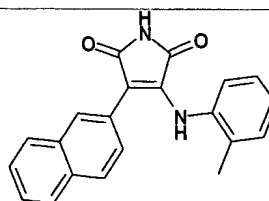
Ex 130



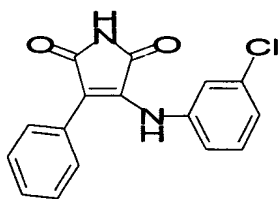
Ex 131



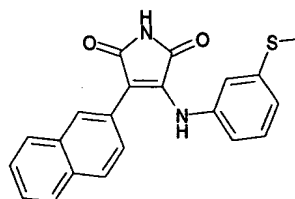
Ex 132



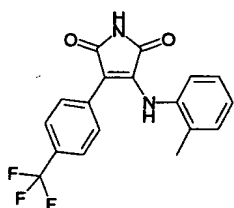
Ex 133



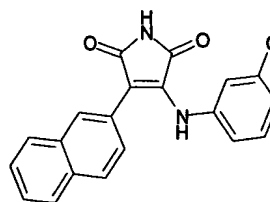
Ex 134



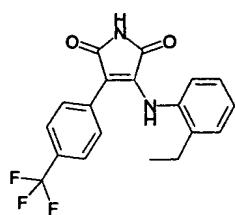
Ex 135



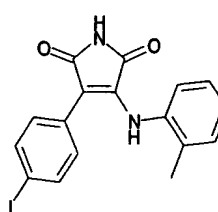
Ex 136



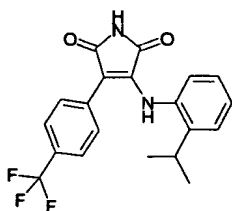
Ex 137



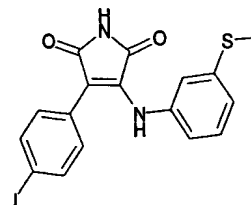
Ex 138



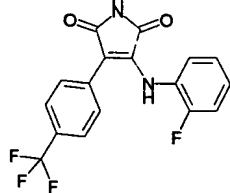
Ex 139



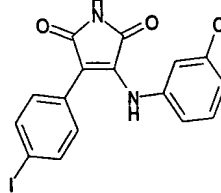
Ex 140



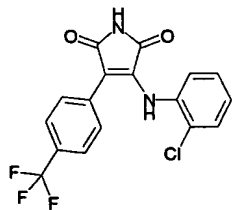
Ex 141



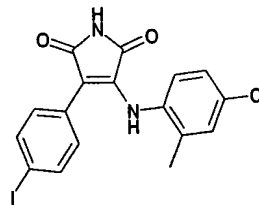
Ex 142



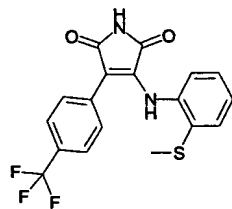
Ex 143



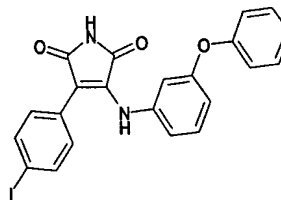
Ex 144



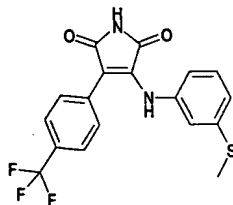
Ex 145



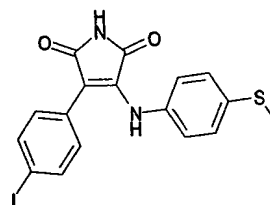
Ex 146



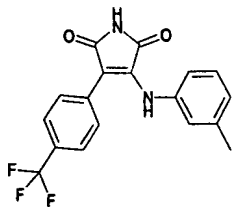
Ex 147



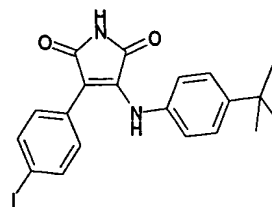
Ex 148



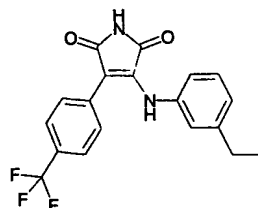
Ex 149



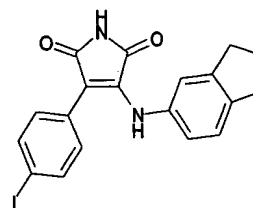
Ex 150



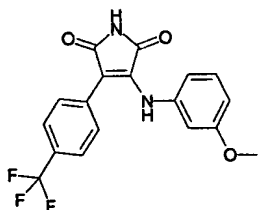
Ex 151



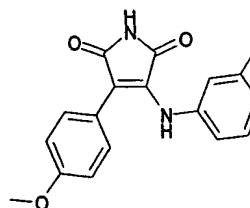
Ex 152



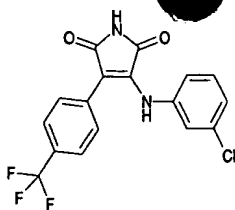
Ex 153



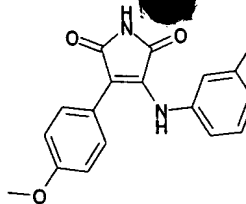
Ex 154



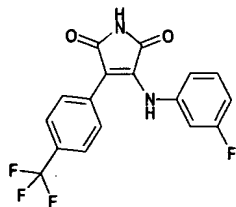
Ex 155



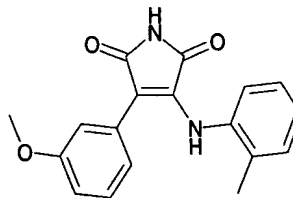
Ex 156



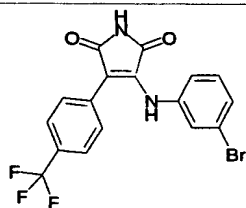
Ex 157



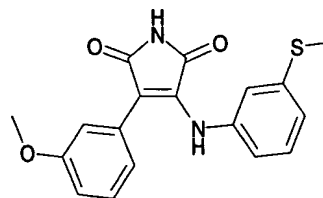
Ex 158



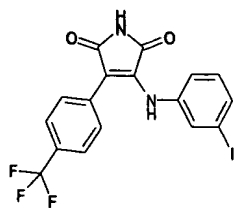
Ex 159



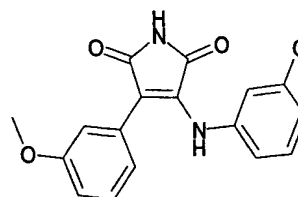
Ex 160



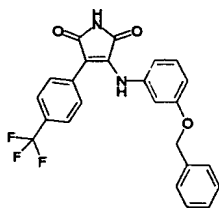
Ex 161



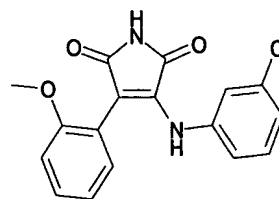
Ex 162



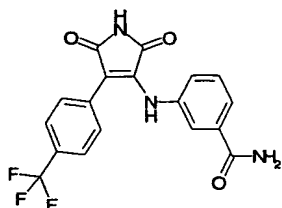
Ex 163



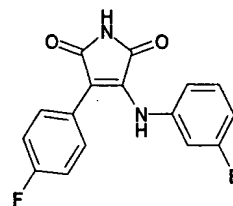
Ex 164



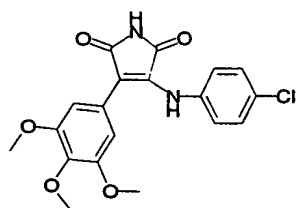
Ex 165



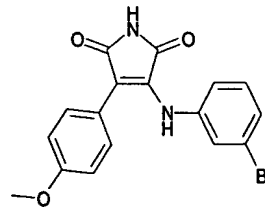
Ex 166



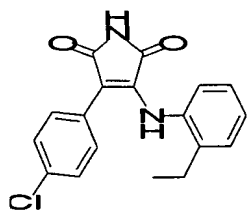
Ex 167



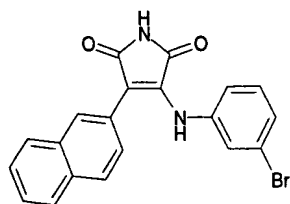
Ex 168



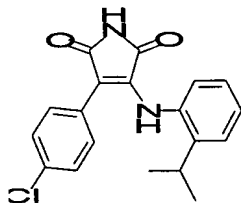
Ex 169



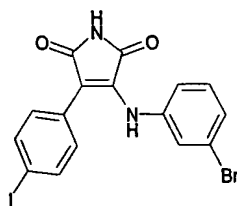
Ex 170



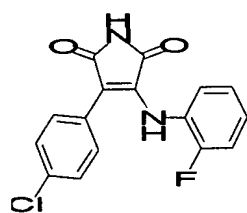
Ex 171



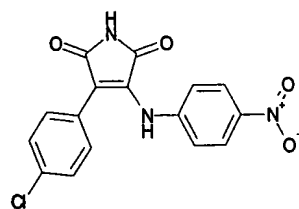
Ex 172



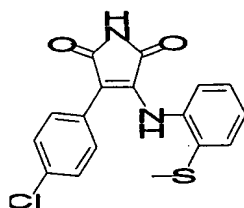
Ex 173



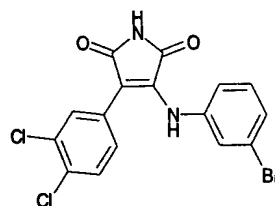
Ex 174



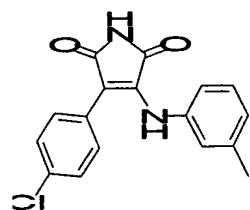
Ex 175



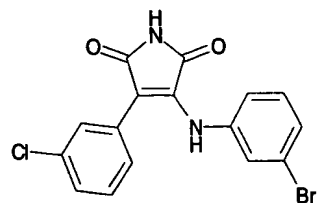
Ex 176



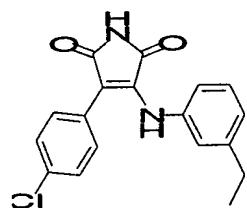
Ex 177



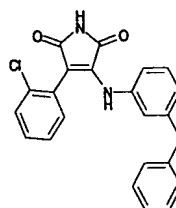
Ex 178



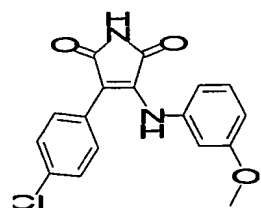
Ex 179



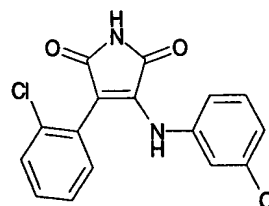
Ex 180

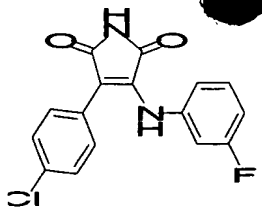
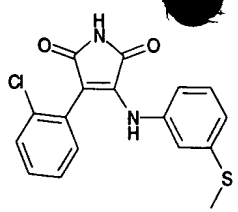
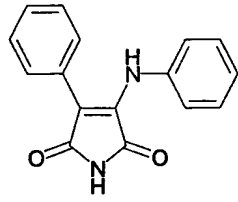
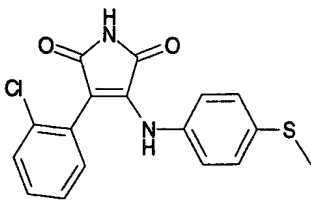
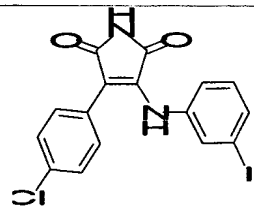
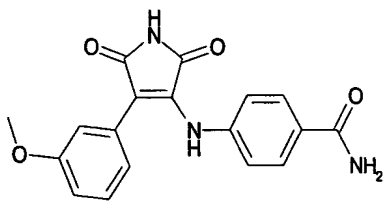
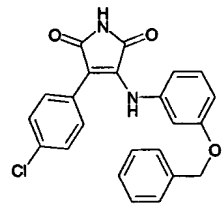
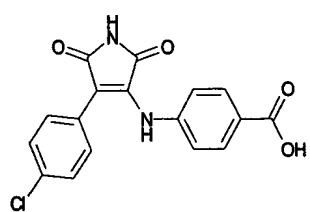
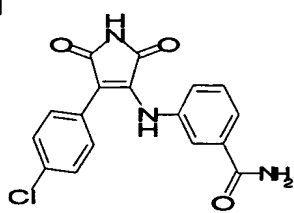
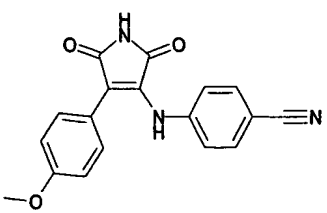
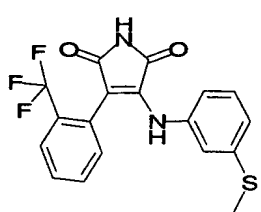
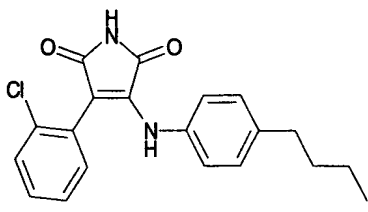
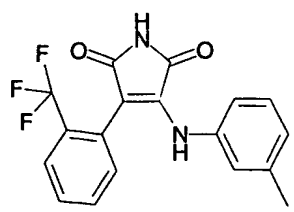
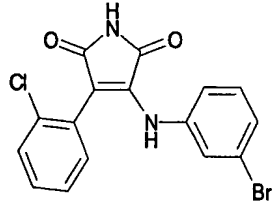


Ex 181

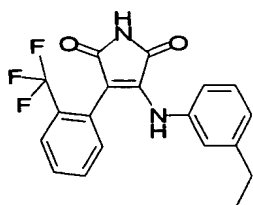


Ex 182

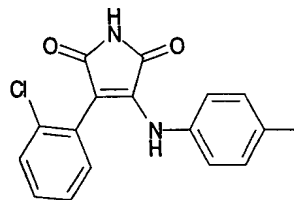


Ex 183 	Ex 184 
Ex 185 	Ex 186 
Ex 187 	Ex 188 
Ex 189 	Ex 190 
Ex 191 	Ex 192 
Ex 193 	Ex 194 
Ex 195 	Ex 196 

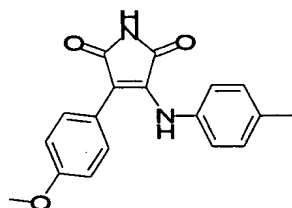
Ex 197



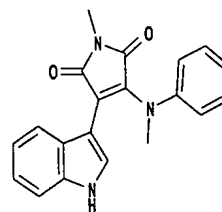
Ex 198



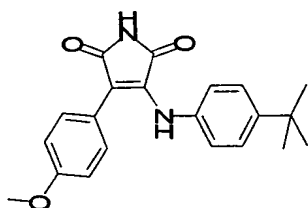
Ex 199



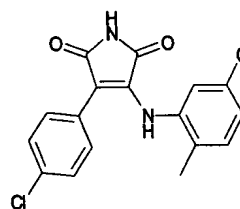
Ex 200



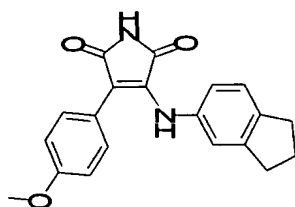
Ex 201



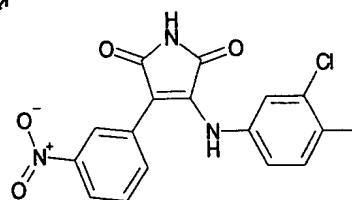
Ex 202



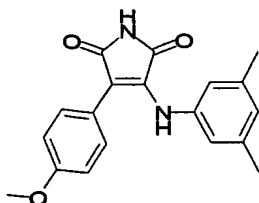
Ex 203



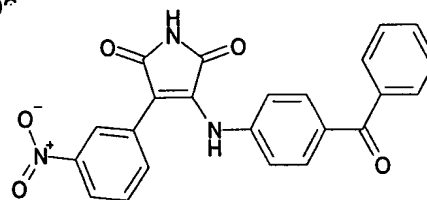
Ex 204



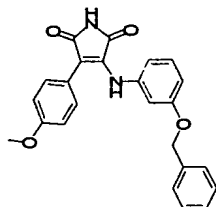
Ex 205



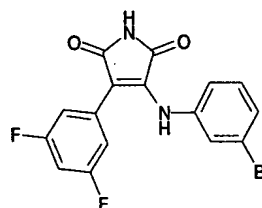
Ex 206



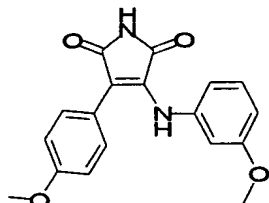
Ex 207



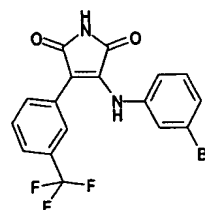
Ex 208



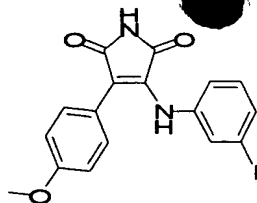
Ex 209



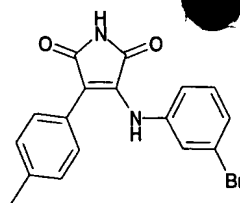
Ex 210



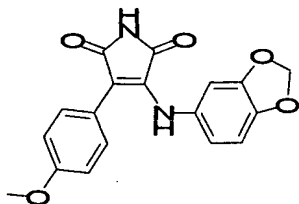
Ex 211



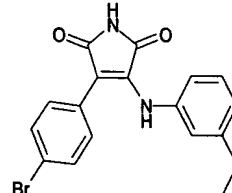
Ex 212



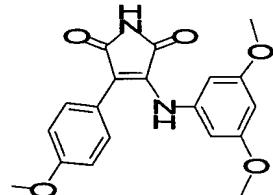
Ex 213



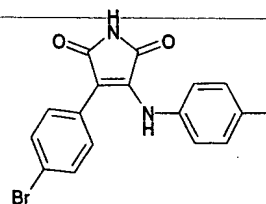
Ex 214



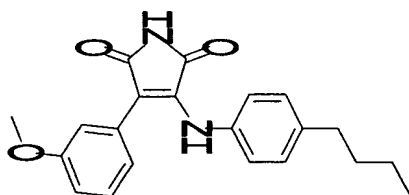
Ex 215



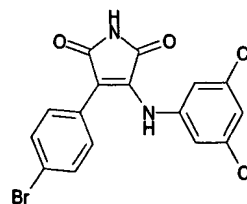
Ex 216



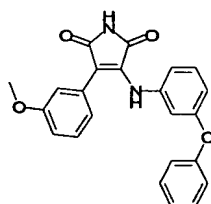
Ex 217



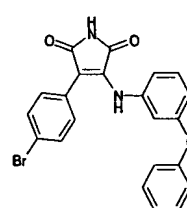
Ex 218



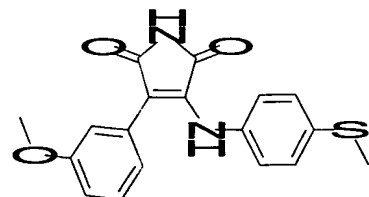
Ex 219



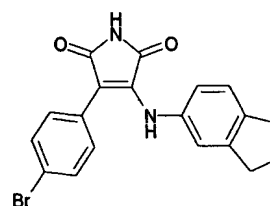
Ex 220



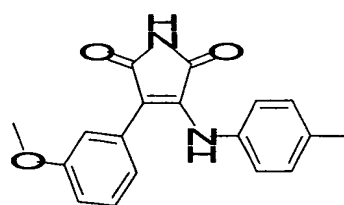
Ex 221



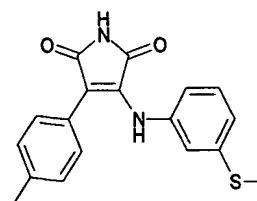
Ex 222



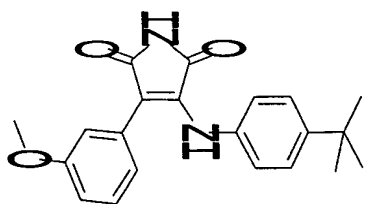
Ex 223



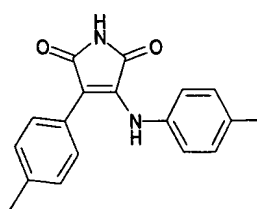
Ex 224



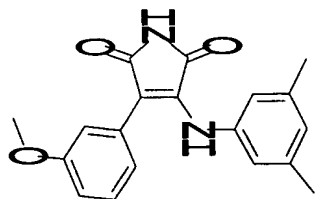
Ex 225



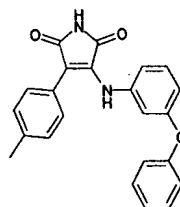
Ex 226



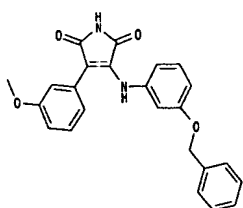
Ex 227



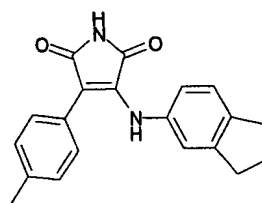
Ex 228



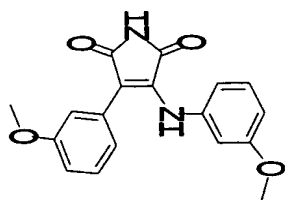
Ex 229



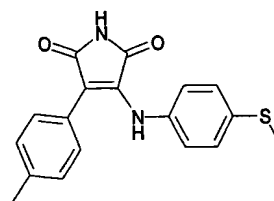
Ex 230



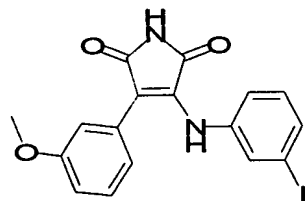
Ex 231



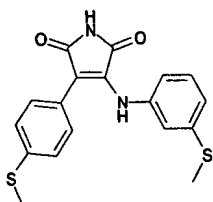
Ex 232



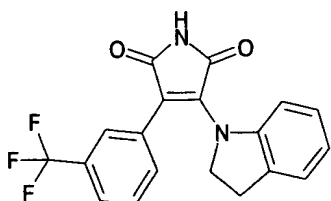
Ex 233



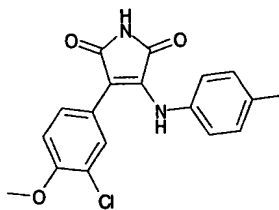
Ex 234



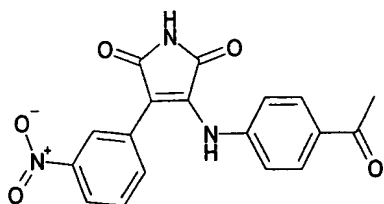
Ex 235



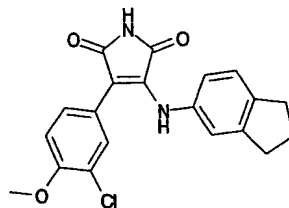
Ex 236



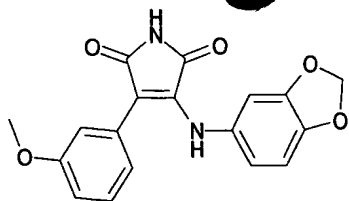
Ex 237



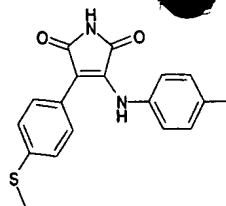
Ex 238



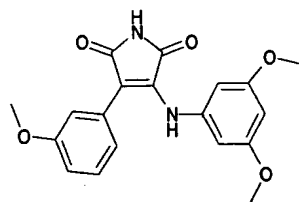
Ex 239



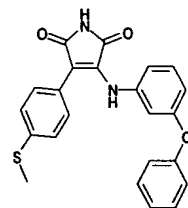
Ex 240



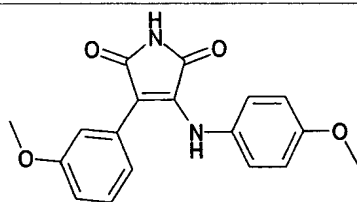
Ex 241



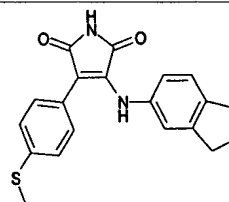
Ex 242



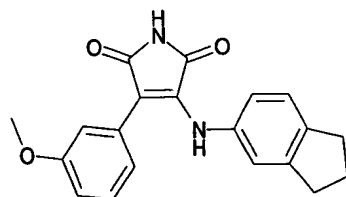
Ex 243



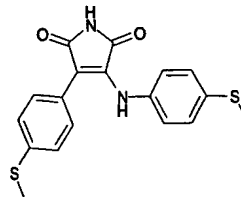
Ex 244



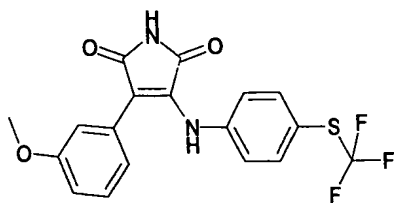
Ex 245



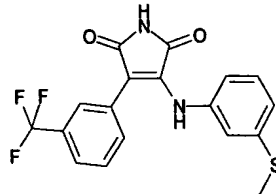
Ex 246



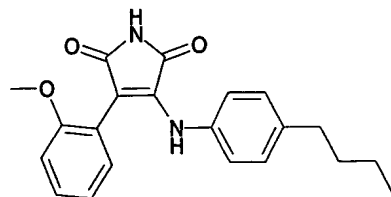
Ex 247



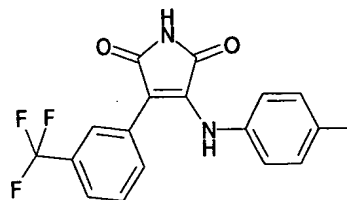
Ex 248



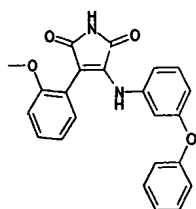
Ex 249



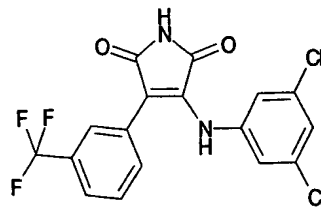
Ex 250



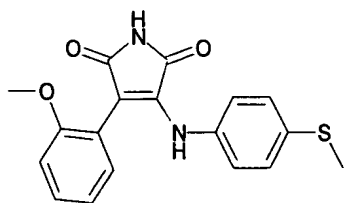
Ex 251



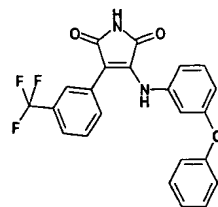
Ex 252



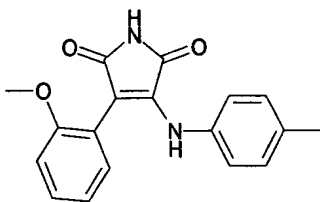
Ex 253



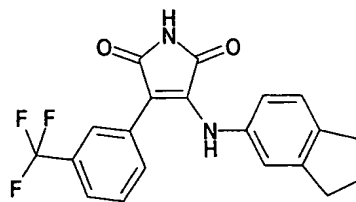
Ex 254



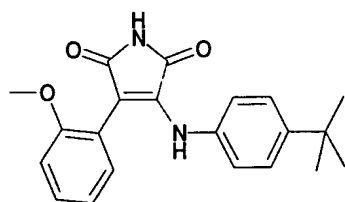
Ex 255



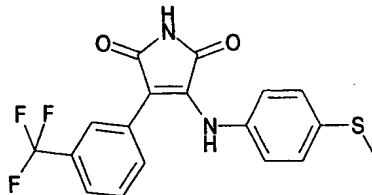
Ex 256



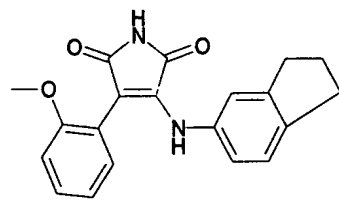
Ex 257



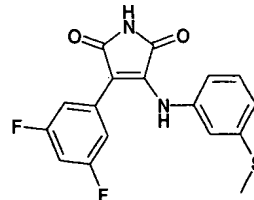
Ex 258



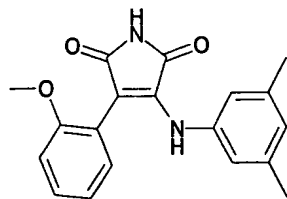
Ex 259



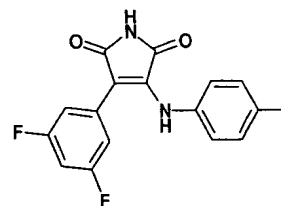
Ex 260



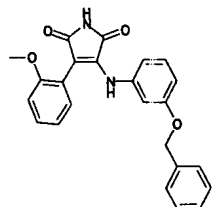
Ex 261



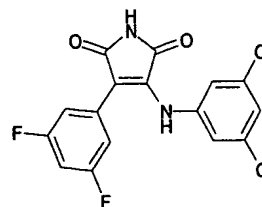
Ex 262



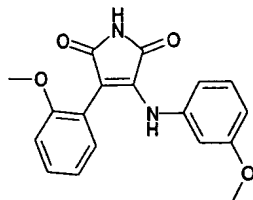
Ex 263



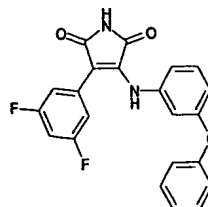
Ex 264



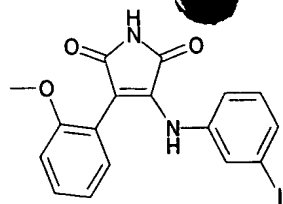
Ex 265



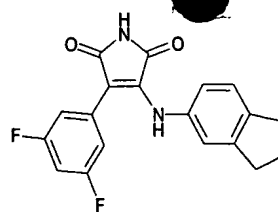
Ex 266



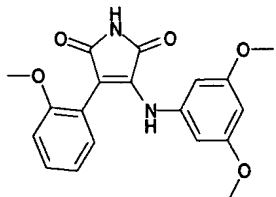
Ex 267



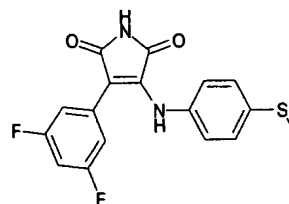
Ex 268



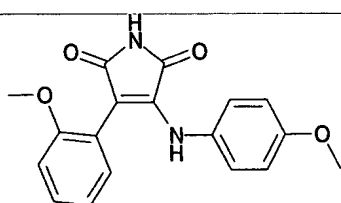
Ex 269



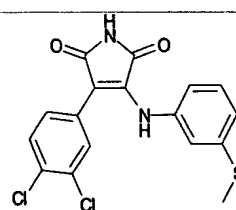
Ex 270



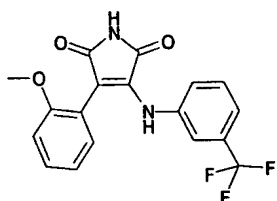
Ex 271



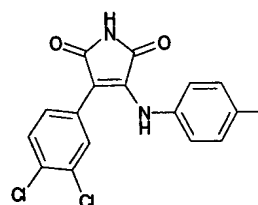
Ex 272



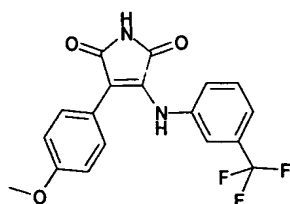
Ex 273



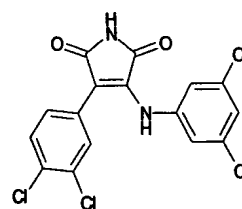
Ex 274



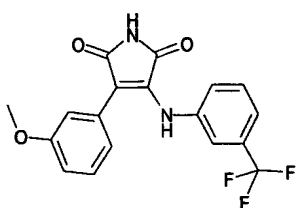
Ex 275



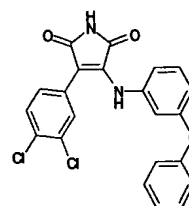
Ex 276



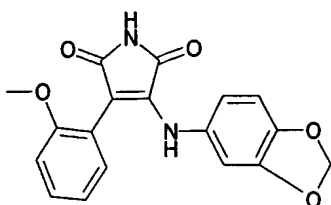
Ex 277



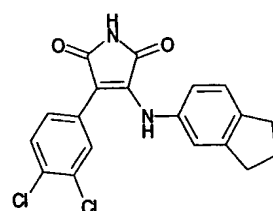
Ex 278



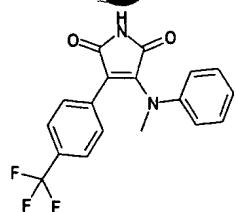
Ex 279



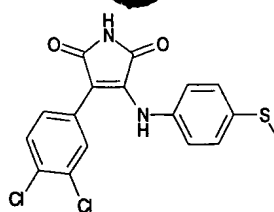
Ex 280



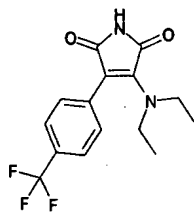
Ex 281



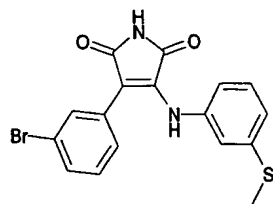
Ex 282



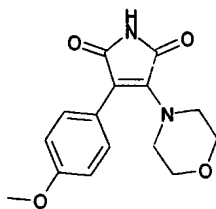
Ex 283



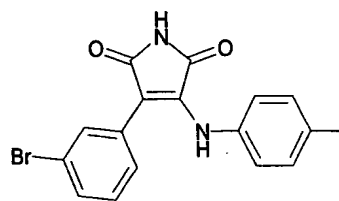
Ex 284



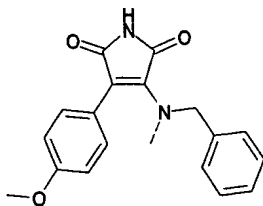
Ex 285



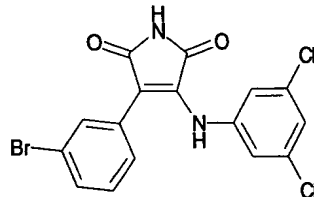
Ex 286



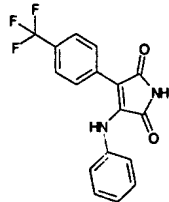
Ex 287



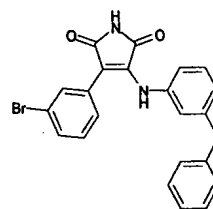
Ex 288



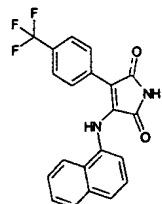
Ex 289



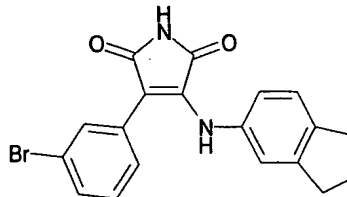
Ex 290



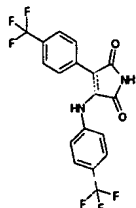
Ex 291



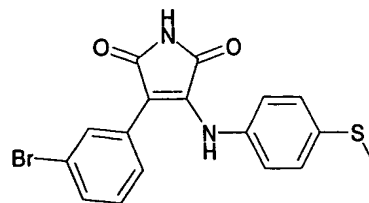
Ex 292



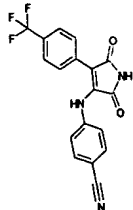
Ex 293



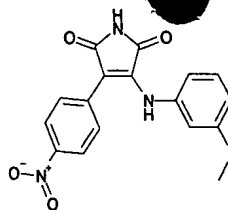
Ex 294



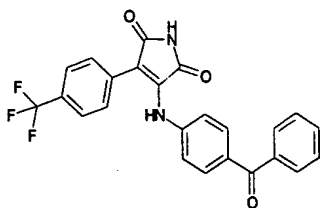
Ex 295



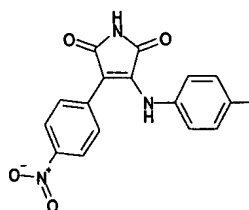
Ex 296



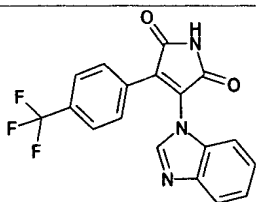
Ex 297



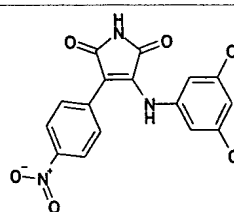
Ex 298



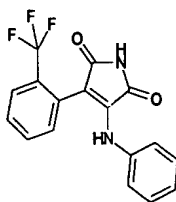
Ex 299



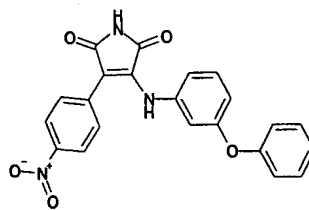
Ex 300



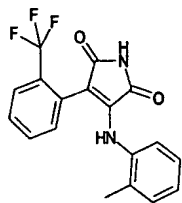
Ex 301



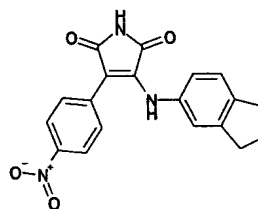
Ex 302



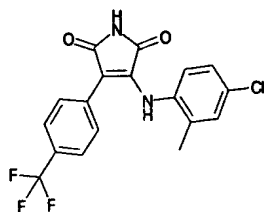
Ex 303



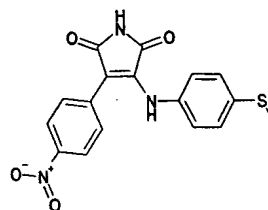
Ex 304



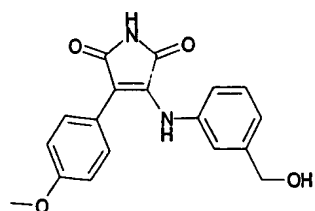
Ex 305



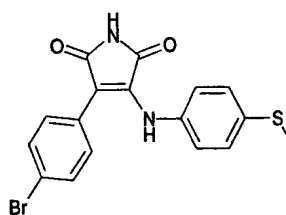
Ex 306



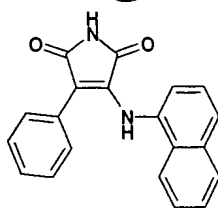
Ex 307



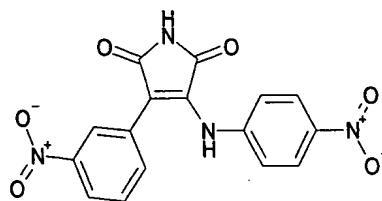
Ex 308



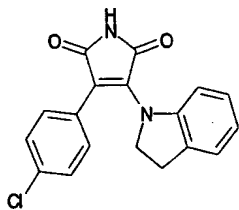
Ex 309



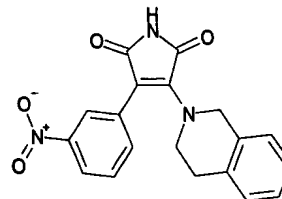
Ex 310



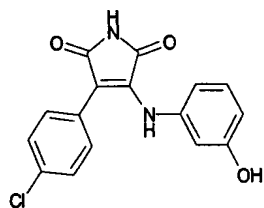
Ex 311



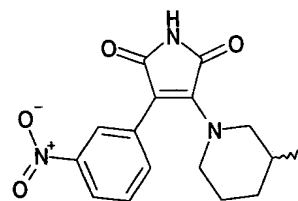
Ex 312



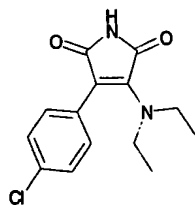
Ex 313



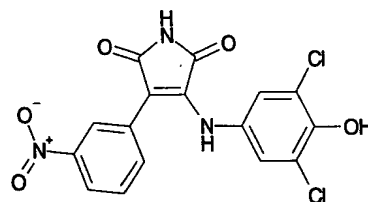
Ex 314



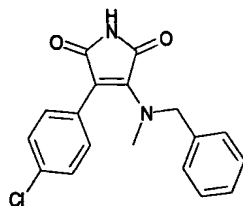
Ex 315



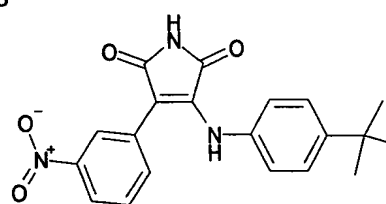
Ex 316



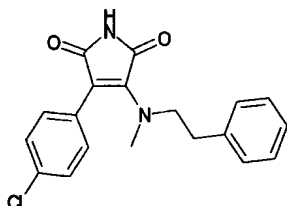
Ex 317



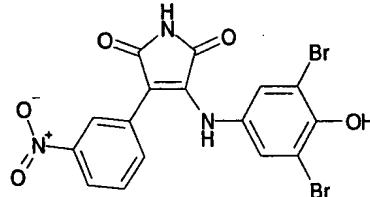
Ex 318



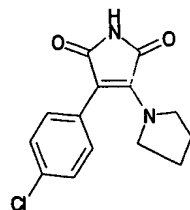
Ex 319



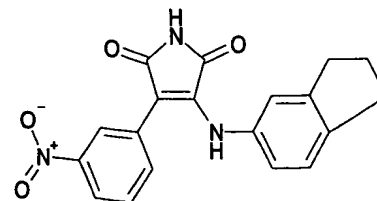
Ex 320



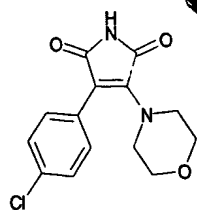
Ex 321



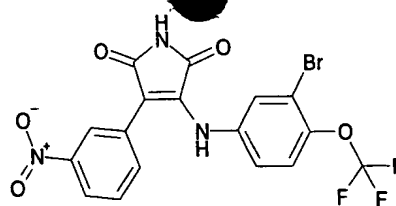
Ex 322



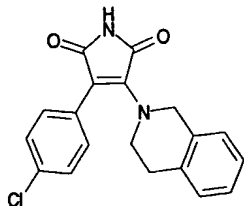
Ex 323



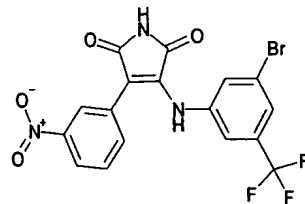
Ex 324



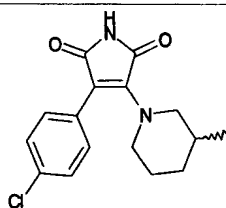
Ex 325



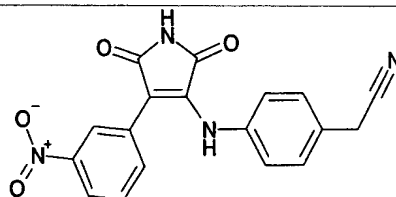
Ex 326



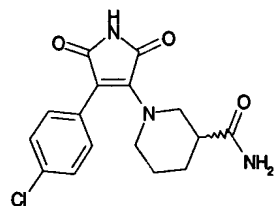
Ex 327



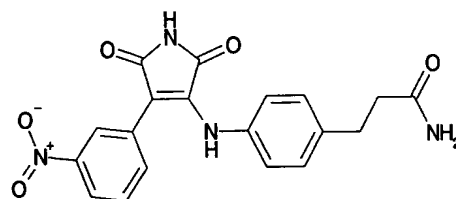
Ex 328



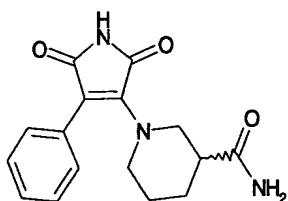
Ex 329



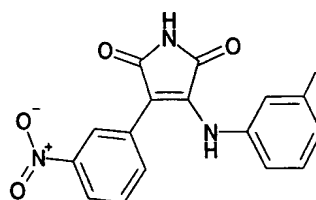
Ex 330



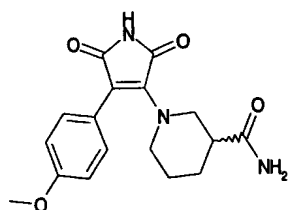
Ex 331



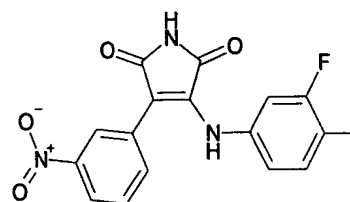
Ex 332



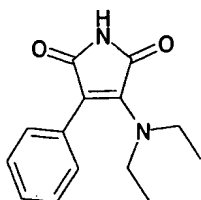
Ex 333



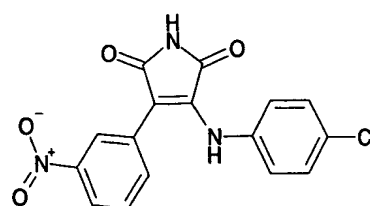
Ex 334



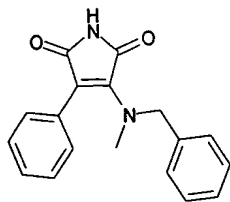
Ex 335



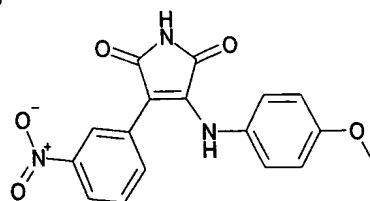
Ex 336



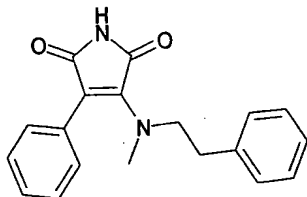
Ex 337



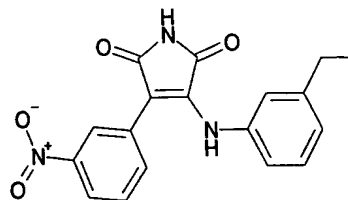
Ex 338



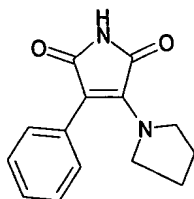
Ex 339



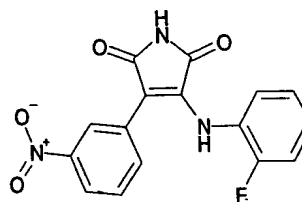
Ex 340



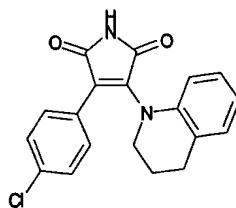
Ex 341



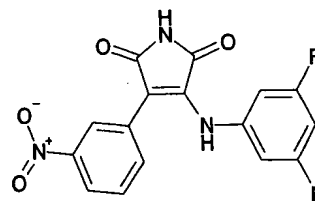
Ex 342



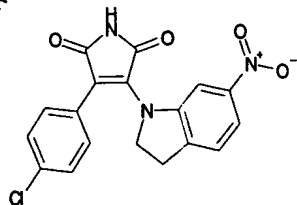
Ex 343



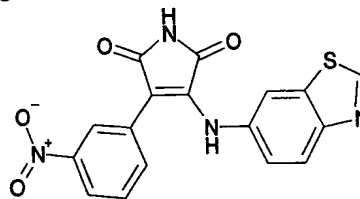
Ex 344



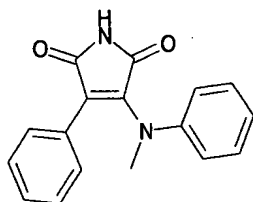
Ex 345



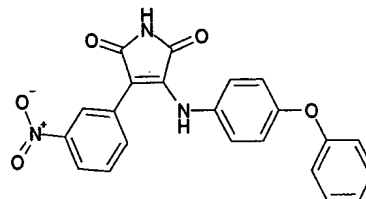
Ex 346



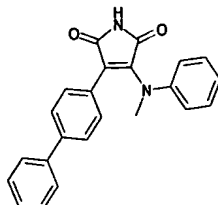
Ex 347



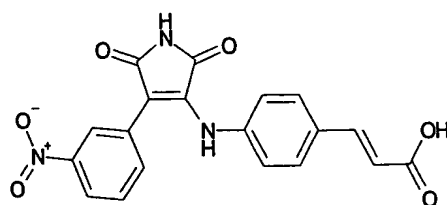
Ex 348



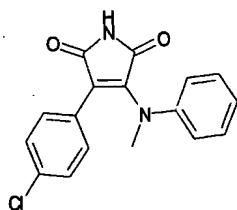
Ex 349



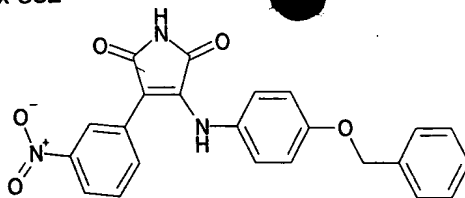
Ex 350



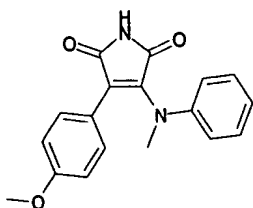
Ex 351



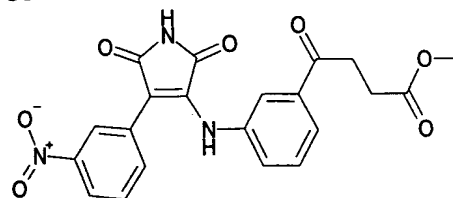
Ex 352



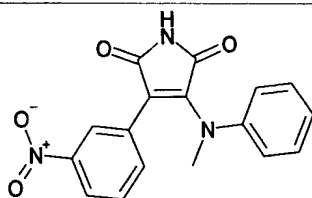
Ex 353



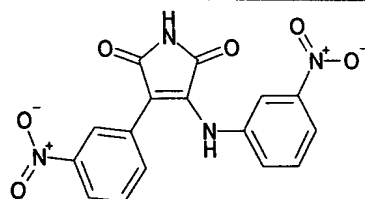
Ex 354



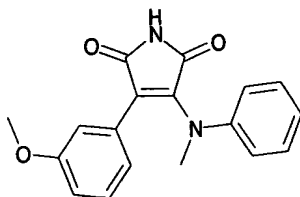
Ex 355



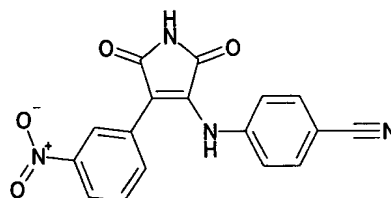
Ex 356



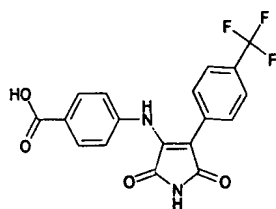
Ex 357



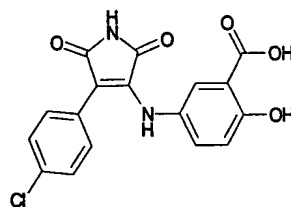
Ex 358



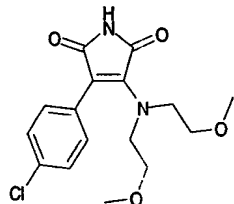
Ex 359



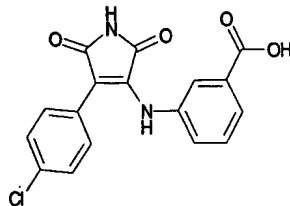
Ex 360



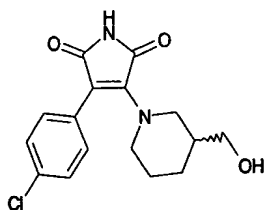
Ex 361



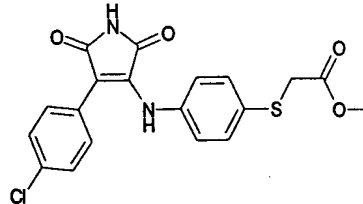
Ex 362



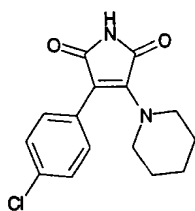
Ex 363



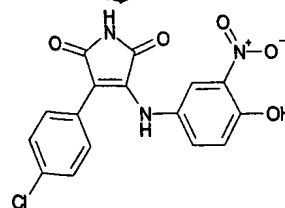
Ex 364



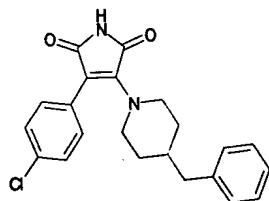
Ex 365



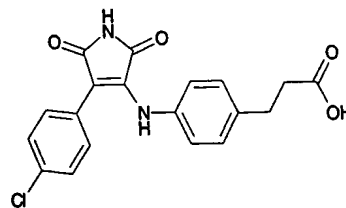
Ex 366



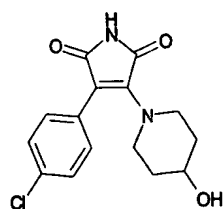
Ex 367



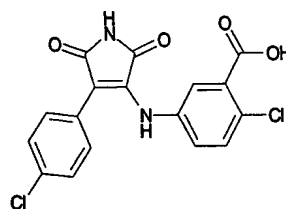
Ex 368



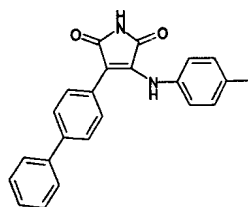
Ex 369



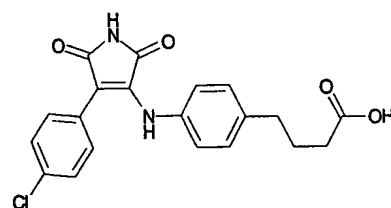
Ex 370



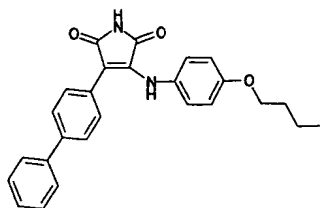
Ex 371



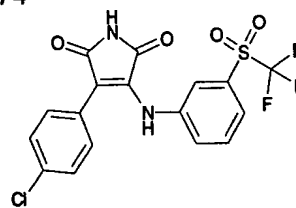
Ex 372



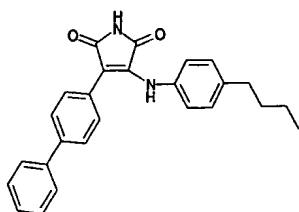
Ex 373



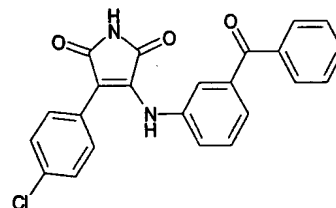
Ex 374



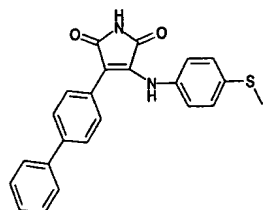
Ex 375



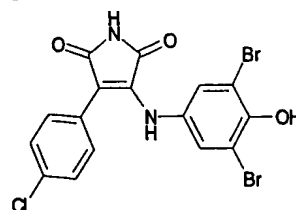
Ex 376

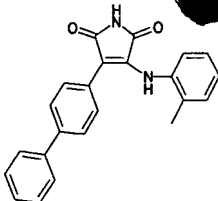
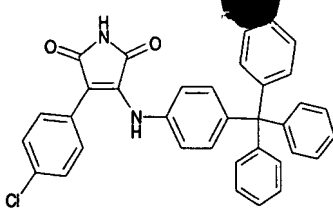
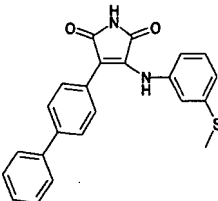
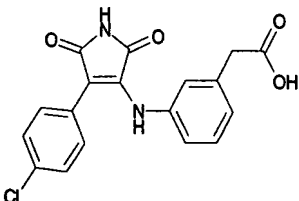
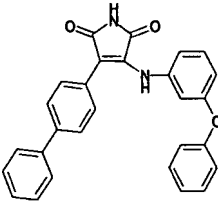
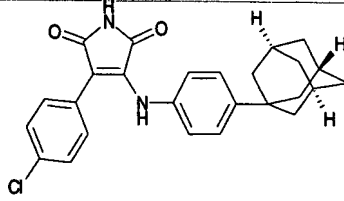
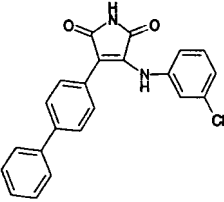
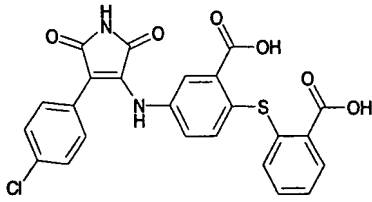
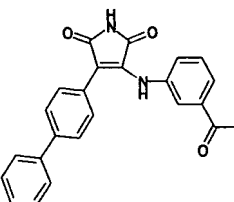
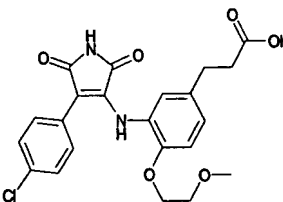
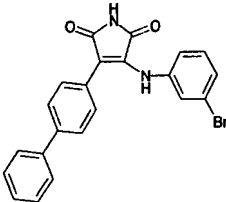
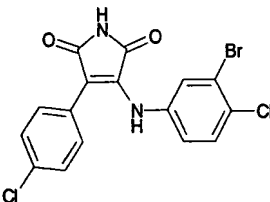
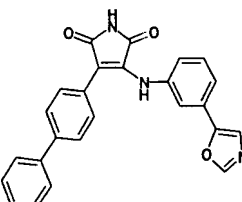
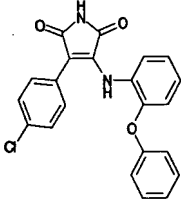


Ex 377

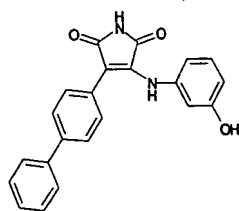


Ex 378

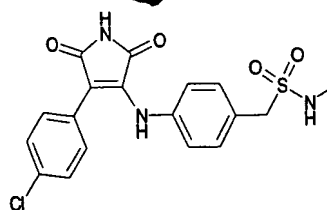


Ex 379 	Ex 380 
Ex 381 	Ex 382 
Ex 383 	Ex 384 
Ex 385 	Ex 386 
Ex 387 	Ex 388 
Ex 389 	Ex 390 
Ex 391 	Ex 392 

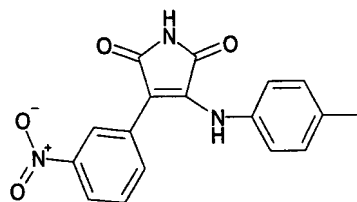
Ex 393



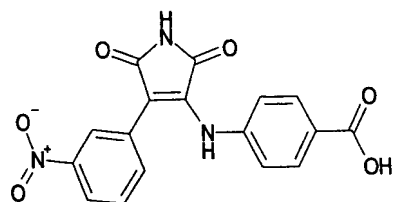
Ex 394



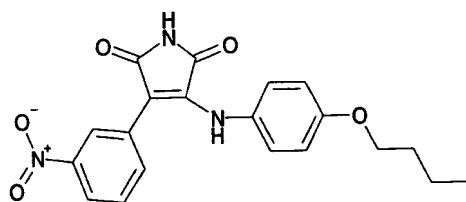
Ex 395



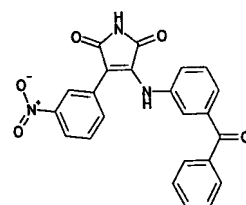
Ex 396



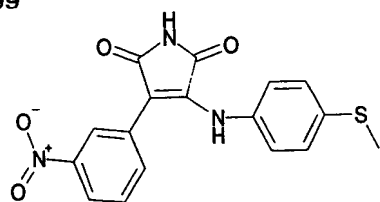
Ex 397



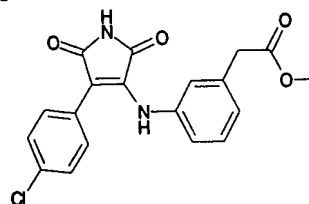
Ex 398



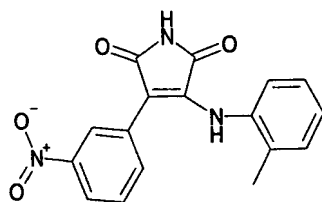
Ex 399



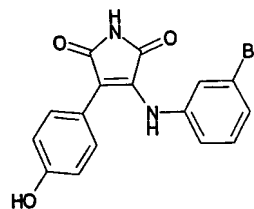
Ex 400



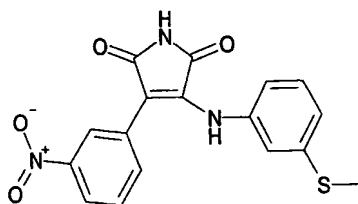
Ex 401



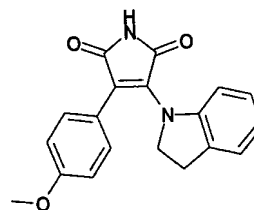
Ex 402



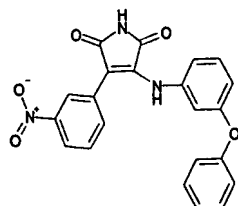
Ex 403



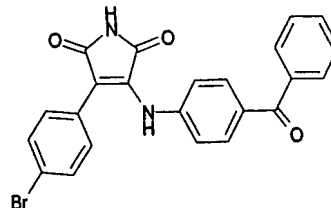
Ex 404

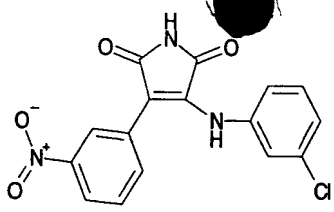
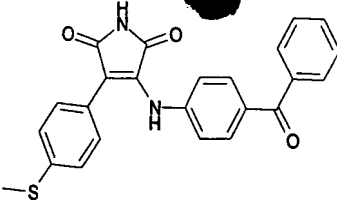
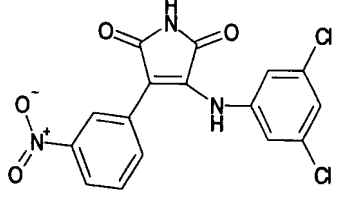
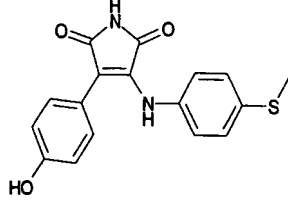
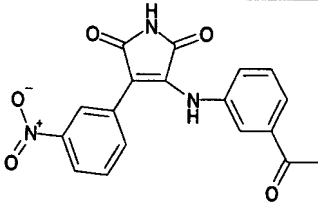
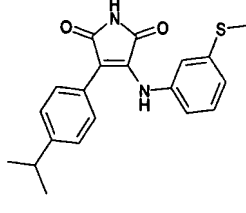
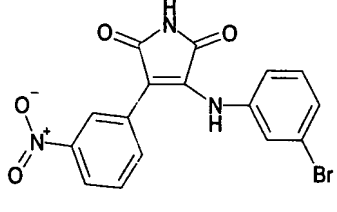
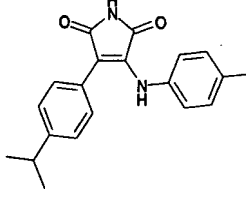
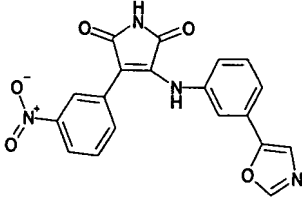
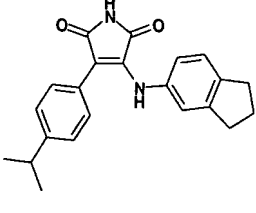
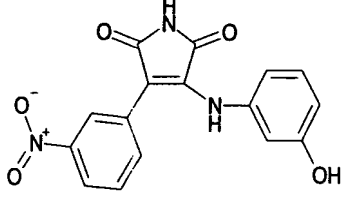
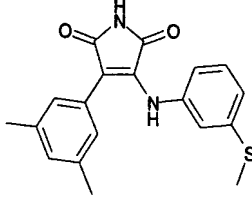
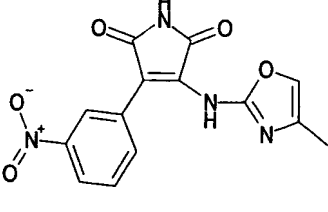
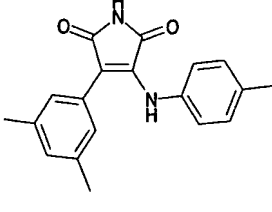


Ex 405

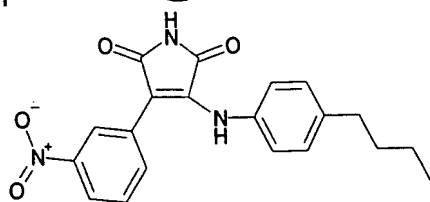


Ex 406

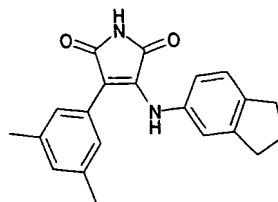


Ex 407 	Ex 408 
Ex 409 	Ex 410 
Ex 411 	Ex 412 
Ex 413 	Ex 414 
Ex 415 	Ex 416 
Ex 417 	Ex 418 
Ex 419 	Ex 420 

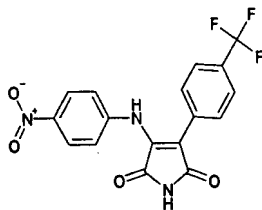
Ex 421



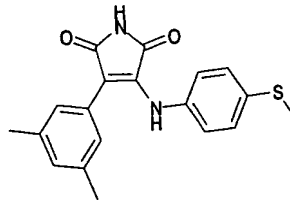
Ex 422



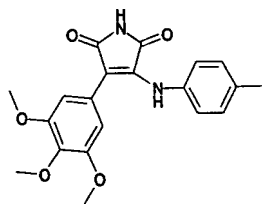
Ex 423



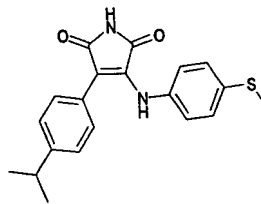
Ex 424



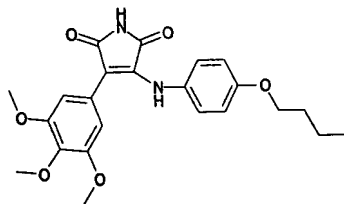
Ex 425



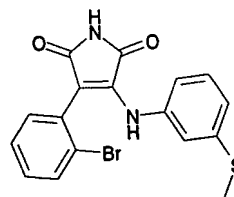
Ex 426



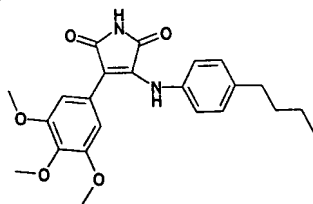
Ex 427



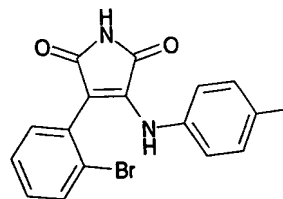
Ex 428



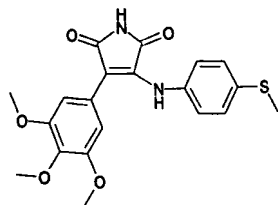
Ex 429



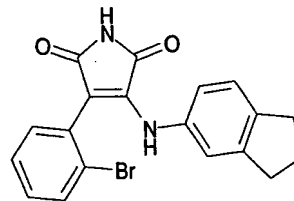
Ex 430



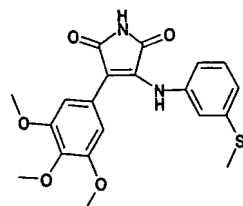
Ex 431



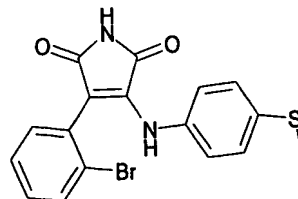
Ex 432

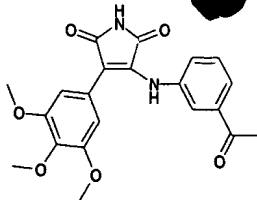
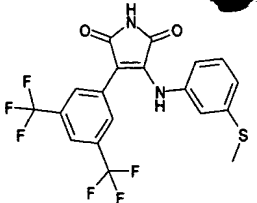
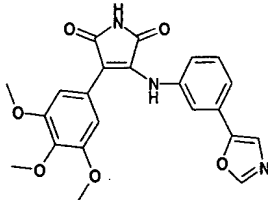
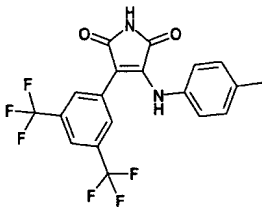
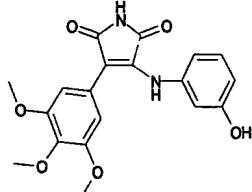
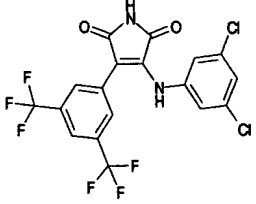
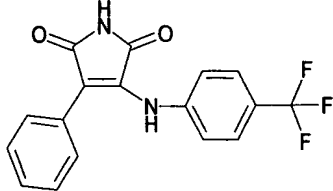
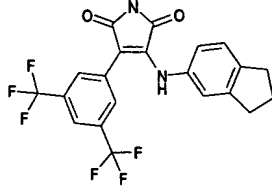
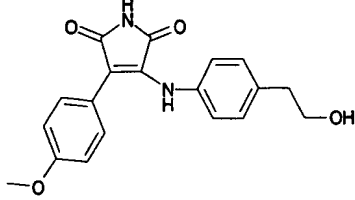
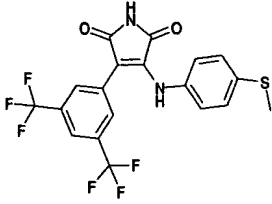
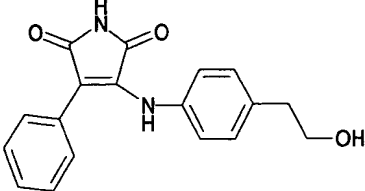
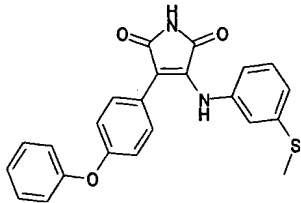
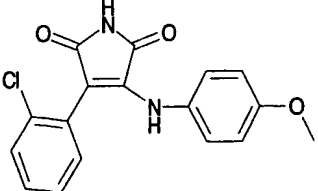
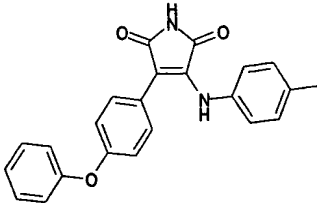


Ex 433

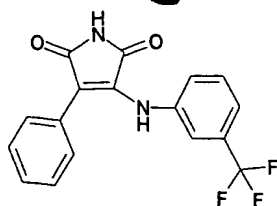


Ex 434

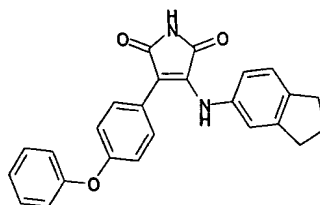


Ex 435 	Ex 436 
Ex 437 	Ex 438 
Ex 439 	Ex 440 
Ex 441 	Ex 442 
Ex 443 	Ex 444 
Ex 445 	Ex 446 
Ex 447 	Ex 448 

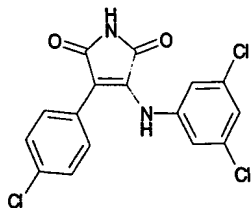
Ex 449



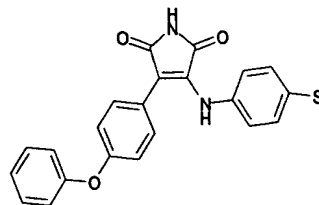
Ex 450



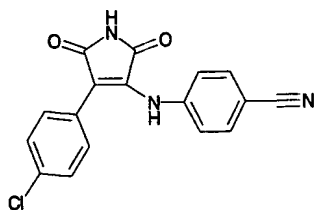
Ex 451



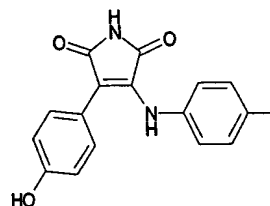
Ex 452



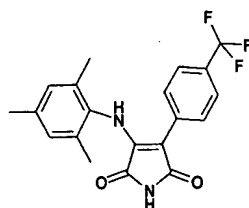
Ex 453



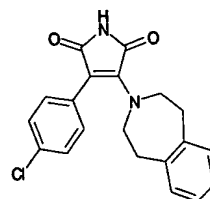
Ex 454



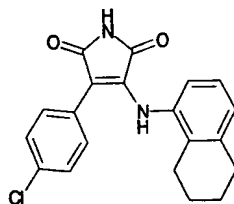
Ex 455



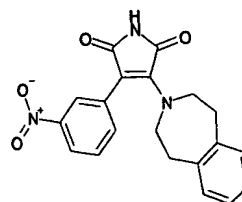
Ex 456



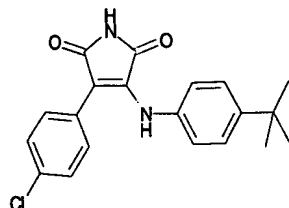
Ex 457



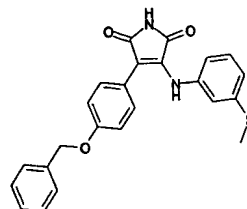
Ex 458



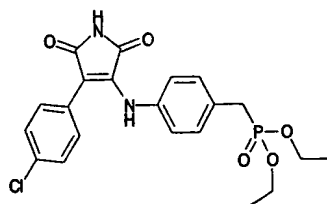
Ex 459



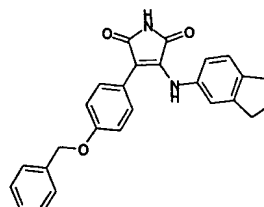
Ex 460



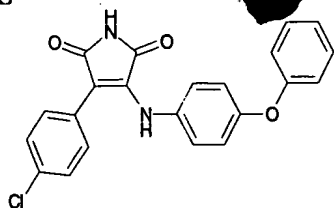
Ex 461



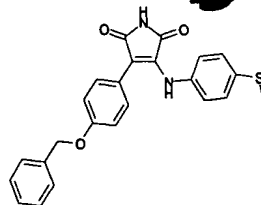
Ex 462



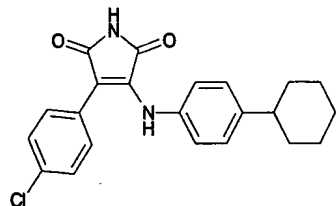
Ex 463



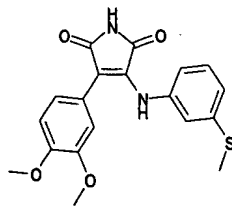
Ex 464



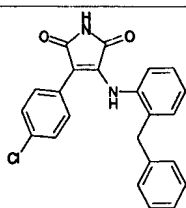
Ex 465



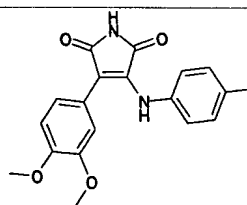
Ex 466



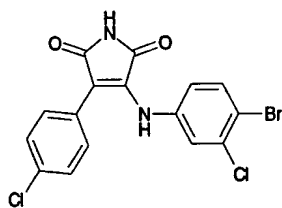
Ex 467



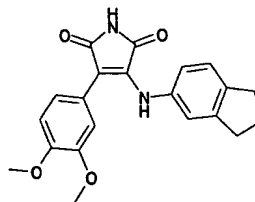
Ex 468



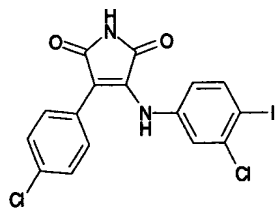
Ex 469



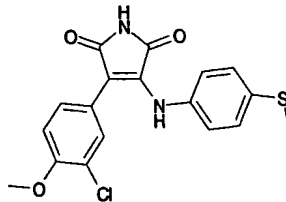
Ex 470



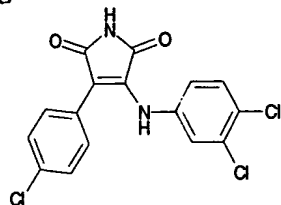
Ex 471



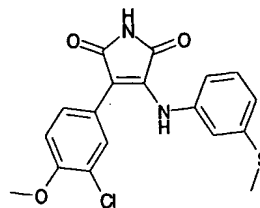
Ex 472



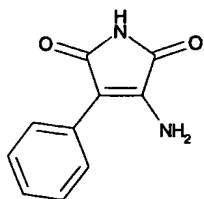
Ex 473



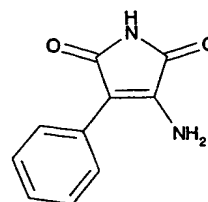
Ex 474



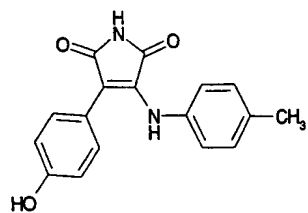
Ex 475



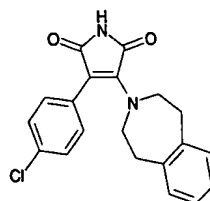
Ex 476



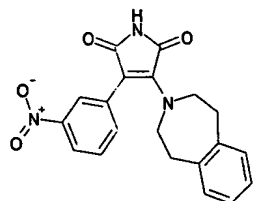
Ex 477



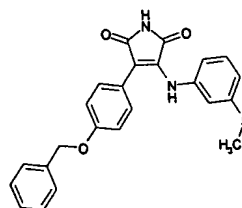
Ex 478



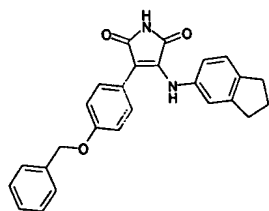
Ex 479



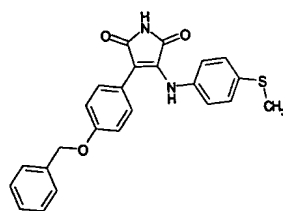
Ex 480



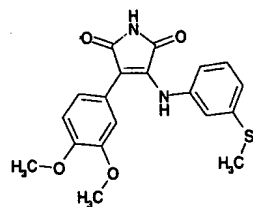
Ex 481



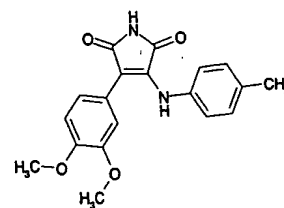
Ex 482



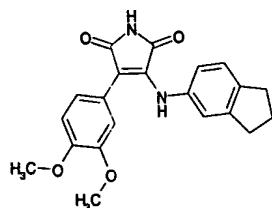
Ex 483



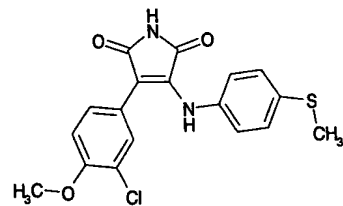
Ex 484



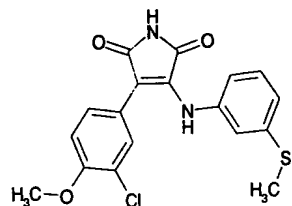
Ex 485



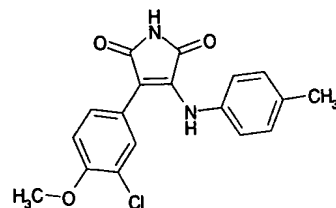
Ex 486



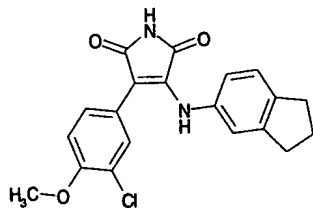
Ex 487



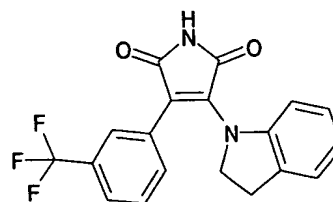
Ex 488

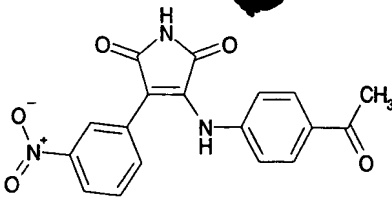
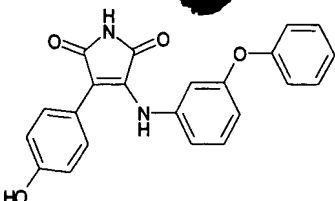
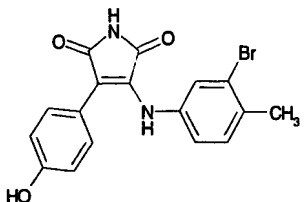
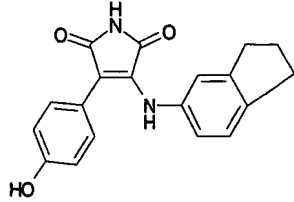
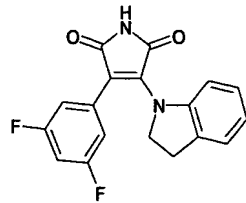
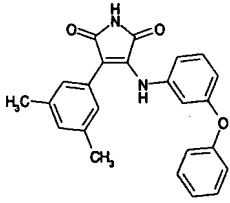
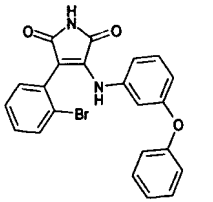
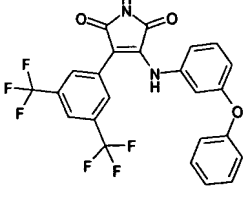
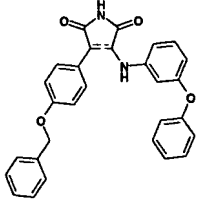
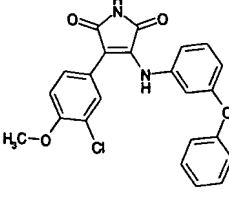
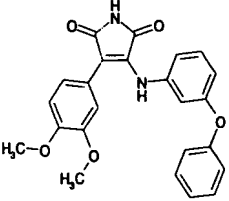
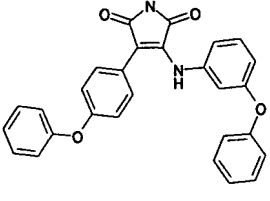
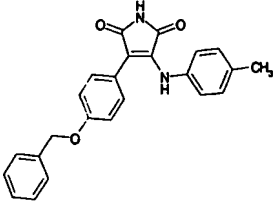
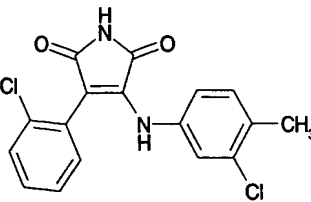


Ex 489

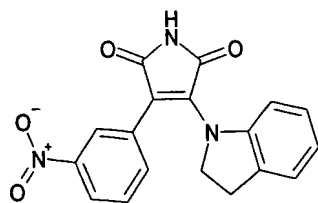


Ex 490

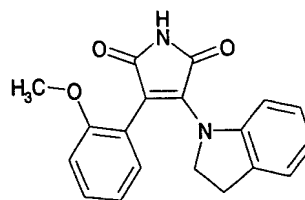


Ex 491 	Ex 492 
Ex 493 	Ex 494 
Ex 495 	Ex 496 
Ex 497 	Ex 498 
Ex 499 	Ex 500 
Ex 501 	Ex 502 
Ex 503 	Ex 504 

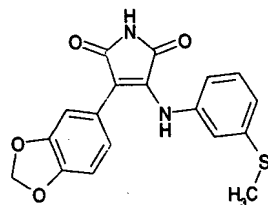
Ex 505



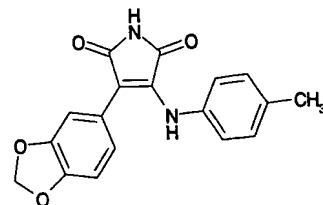
Ex 506



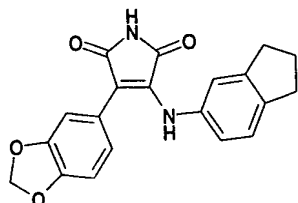
Ex 507



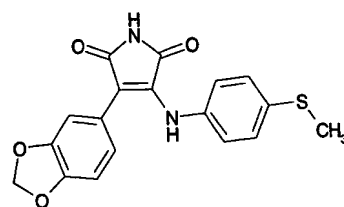
Ex 508



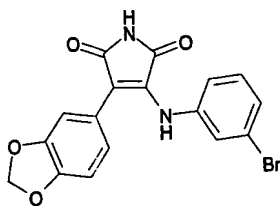
Ex 509



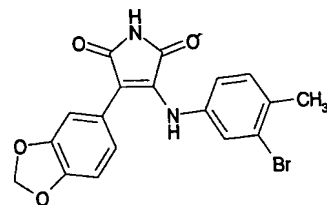
Ex 510



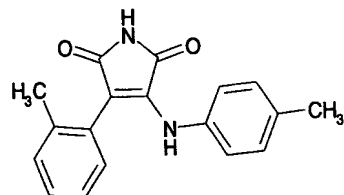
Ex 511



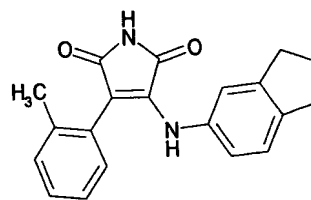
Ex 512



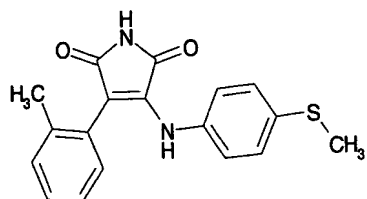
Ex 513



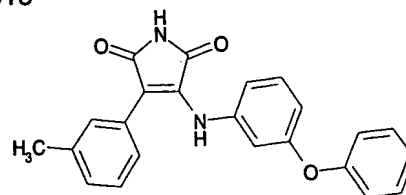
Ex 514



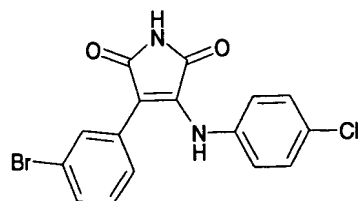
Ex 515



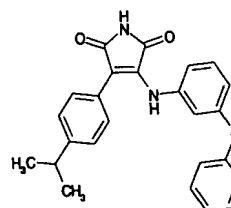
Ex 516



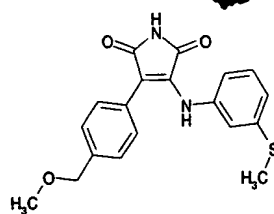
Ex 517



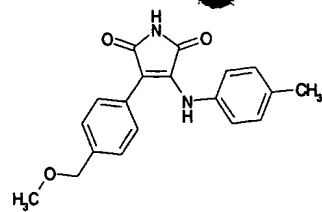
Ex 518



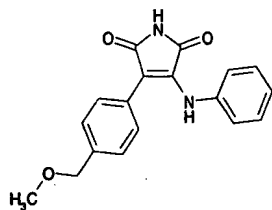
Ex 519



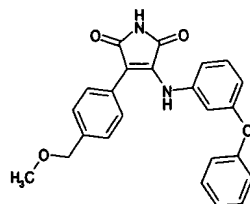
Ex 520



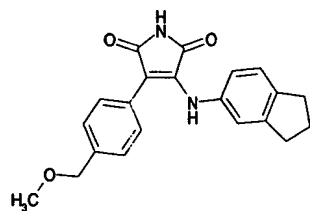
Ex 521



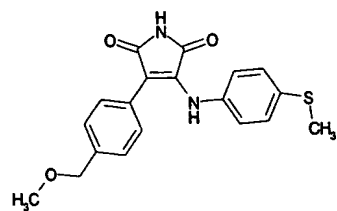
Ex 522



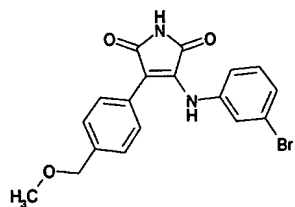
Ex 523



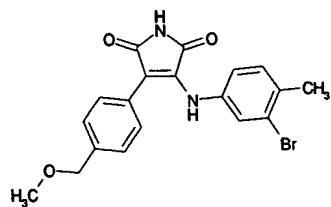
Ex 524



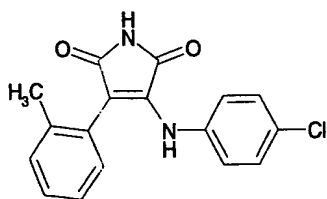
Ex 525



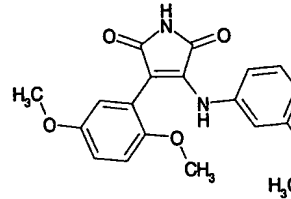
Ex 526



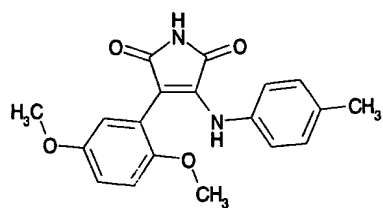
Ex 527



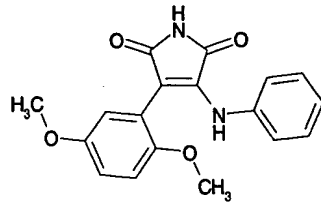
Ex 528



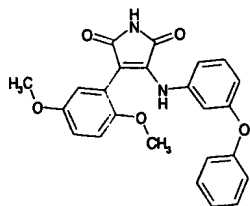
Ex 529



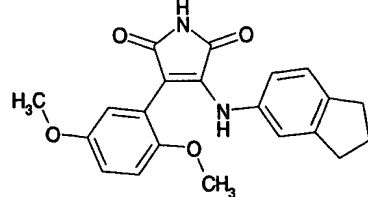
Ex 530



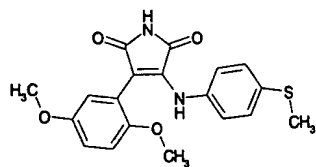
Ex 531



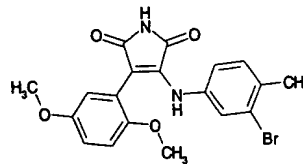
Ex 532



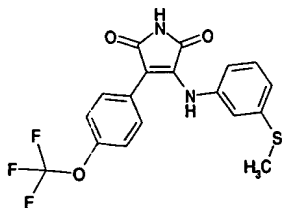
Ex 533



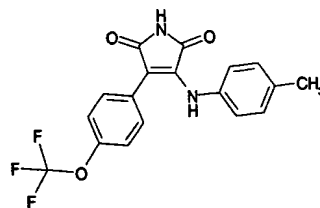
Ex 534



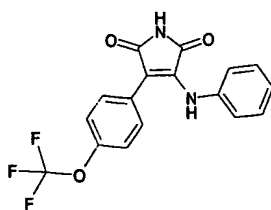
Ex 535



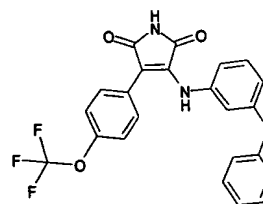
Ex 536



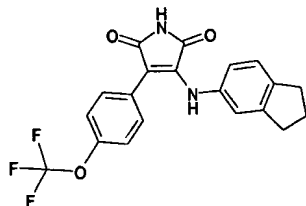
Ex 537



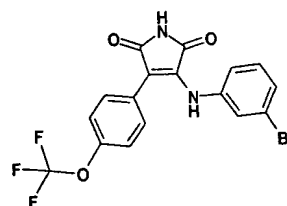
Ex 538



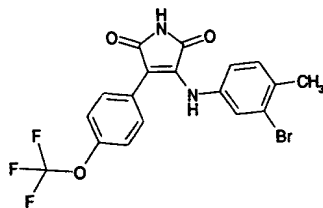
Ex 539



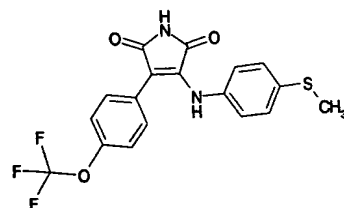
Ex 540



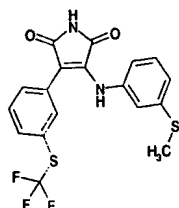
Ex 541



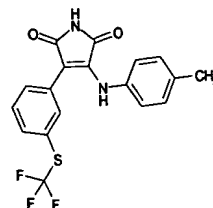
Ex 542



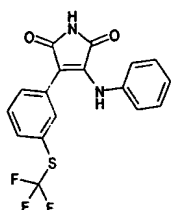
Ex 543



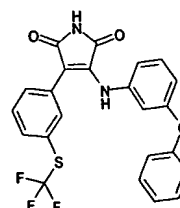
Ex 544



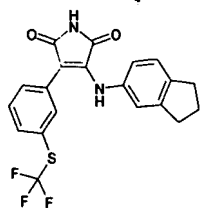
Ex 545



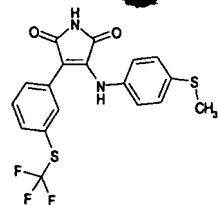
Ex 546



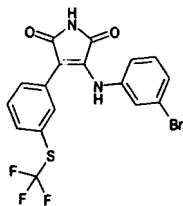
Ex 547



Ex 548



Ex 549



Ex 550

